Treatment of Hidradenitis Suppurativa Evaluation Study (THESEUS): a prospective cohort study

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Funding sources: THESEUS was funded by the NIHR Health Technology Assessment (HTA) grant 17/98/01. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

Conflicts of Interest: JRI receives a stipend as Editor-in-Chief of the British Journal of Dermatology and an authorship honorarium from UpToDate. He is a consultant for Abbvie, Boehringer Ingelheim, ChemoCentryx, Citryll, Novartis and UCB Pharma and has served on advisory boards for Insmed, Kymera Therapeutics and Viela Bio. He is co-copyright holder of HiSQOL, Investigator Global Assessment and Patient Global Assessment instruments for HS. His department receives income from copyright of the Dermatology Life Quality Instrument (DLQI) and related instruments. LH has received consultancy fees from the University of Oxford for an educational grant funded by Pfizer, unrelated to the submitted work. KH is a member of the NHR HTA General Committee (2016–2022), the NIHR HTA Funding Committee Policy Group (2017–2022) and the NIHR Research Professors Panel (2019–present). RCJ was a NHR HTA Associate Board Member (May 2018 to March 2020). FC is a consultant for UCB Pharma and received a fee from Daylong for participating in a hidradenitis suppurativa consensus meeting.

Data availability: All data requests should be submitted for consideration to: ctrdatasamplerequests@cardiff.ac.uk. Access to anonymised data may be granted following review.

Ethics statement: The Wales Research Ethics Committee 4 provided ethical approval for THESEUS on 26 September 2019, reference number 19/WA/0263.

What is already known about this topic?

- There is a relative lack of evidence for the efficacy, tolerance, and patient acceptability of many of the commonly used treatments for hidradenitis suppurativa (HS)
- The HS Priority Setting Partnership highlighted a top 10 set of research priorities to take forward
- Deroofing and laser treatment targeting the hair follicle are rarely performed for HS in the UK but feature in HS treatment guidelines in other parts of the world

What does this study add?

- THESEUS established laser and deroofing treatment protocols for HS in the UK
- Favourable recruitment and attrition rates were established for future HS studies
- Laser and deroofing had the highest rates of patient willingness and clinician assessed eligibility to receive treatment compared with conventional surgery, oral clindamycin and rifampicin, or oral doxycycline

Abstract

Background:

Hidradenitis suppurativa (HS) is a chronic, painful disease affecting flexures and other skin regions, producing nodules, abscesses and skin tunnels. Laser treatment targeting hair follicles and deroofing of skin tunnels are standard HS interventions in some countries but rarely offered in the UK.

Objectives:

To describe current UK HS management pathways and influencing factors to inform the design of future randomised controlled trials (RCTs).

Methods:

THESEUS was a non-randomised 12-month prospective cohort study set in 10 UK hospitals offering five interventions: oral doxycycline 200mg daily; oral clindamycin and rifampicin both 300mg twice daily for 10 weeks, extended for longer in some cases; laser treatment targeting hair follicles; deroofing, and conventional surgery. Primary outcome was the combination of clinician-assessed eligibility and participant hypothetical willingness to receive each intervention. Secondary outcomes: proportion of participants selecting each intervention as their final treatment option; proportion who switch treatments; treatment fidelity, and attrition rates.

THESEUS was prospectively registered on ISRCTN Registry: ISRCTN69985145.

Results:

The recruitment target of 150 participants was met after 18 months, in July 2021, with two pauses due to the Covid-19 pandemic. Baseline demographics reflected the HS secondary care population: average age 36 years, 81% female, 20% non-white, 64% current or ex-smokers, 86% BMI≥25, 68% moderate disease, 19% severe, and 13% mild disease. Laser was the intervention with the highest proportion (69%) of participants eligible and willing to receive treatment, then deroofing (58%), conventional surgery (54%), clindamycin and rifampicin (44%), and doxycycline (37%). Laser was ranked first choice by the greatest proportion of participants (41%). Attrition rates were 11% and 17% after three and six months respectively. Concordance with doxycycline was 52% after three months due to lack of efficacy, participant choice and adverse effects. Delays with procedural interventions were common, with only 43% and 26% of participants starting laser and deroofing respectively after three months. Uptake of conventional surgery was too small to characterise the intervention. Switching treatment was uncommon and there were no serious adverse events.

Conclusions:

THESEUS established laser treatment and deroofing for HS in the UK and demonstrated their popularity with patients and clinicians for future RCTs.

Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that can have a large impact on quality of life due to pain, discharge of pus, and scarring.[1] It is characterised by nodules, abscesses and skin tunnels (also known as sinus tracts or fistulae) typically occurring in flexural sites such as the axilla and groin, as well as non-flexural sites.[2] If left untreated, disease severity can progress from intermittent inflammatory lesions to multiple chronically inflamed scars. Management involves integration of medical therapy to reduce the inflammation and surgery to remove irreversible scarring.[3]

A Cochrane review of interventions for HS found that there were relatively few HS randomised controlled trials (RCTs) to guide patient care.[4] Since then, the pharmaceutical industry has initiated several RCTs investigating biologic therapies for HS, however biologic therapy is relatively expensive and is currently located towards the end of the HS treatment pathway.[5,6] There is less trial activity involving surgery, laser and medical therapies such as antibiotics that are routinely used in HS but for which the evidence base remains relatively limited.

The design of the Treatment of Hidradenitis Suppurativa Evaluation Study (THESEUS) was influenced by several factors. Firstly, a James Lind Alliance-supported Priority Setting Partnership (PSP) for HS identified and prioritised a top 10 list of HS research uncertainties.[7] Several of the uncertainties were incorporated into THESEUS, including: "what is the most effective and safe group of oral treatments in treating HS (ranked number one priority); what is the impact of HS and the treatments on people with HS (ranked third) and what is the best surgical procedure to perform in treating HS (ranked sixth)".

Secondly, the UK National Institute for Health Research (NIHR) Health Technology Assessment (HTA) funding body issued a call for studies to investigate "What are the best management options for hidradenitis suppurativa (HS) when first line treatments fail?" The funding brief recommended a cohort study to lay the groundwork for future publicly funded RCTs.

Thirdly, THESEUS was designed to introduce laser treatment and deroofing as HS interventions into the UK. Several RCTs comparing the left and right sides of an affected skin region provide evidence for laser treatment targeting the hair follicle[8,9] and appropriate laser services are available in the UK. However, prior to THESEUS, laser was very rarely used for HS therapy, in part due to funding issues, despite its potential role to treat active lesions and to prevent further lesions. Deroofing is a procedure usually performed under local anaesthetic which involves blunt probing of skin tunnels to identify all the branches and then removing the roof to allow the base to heal by secondary intention.[10] It is a tissue conserving procedure that reduces healing times compared to wide excision and can be performed by dermatologists and surgeons straightforwardly in a procedure room, but was not being performed in the UK prior to THESEUS despite being included in the European HS treatment guidelines.[6]

In planning THESEUS, surveys were sent to dermatologists,[11] surgeons[12] and General Practitioners (GPs)[13] to confirm HS treatments and pathways of care in use in the UK at the time. The surveys demonstrated considerable variation in HS care likely to result in inequality of access to treatment and poorer outcomes for some UK residents with HS depending on their geographical location.

The objectives of the prospective cohort component of THESEUS were to: (i) understand current HS patient pathways and what influences treatment choices to inform the design of future RCTs; (ii) determine the feasibility of recruiting individuals with HS into UK clinical trials; and (iii) fully characterise

the THESEUS drug and procedural interventions. Additional objectives to test the feasibility and responsiveness of outcome measure instruments (OMIs) for HS trials and explore consensus-agreed recommendations for future RCT study designs are covered in other publications.[14,15]

Methods

Study design

The full protocol for THESEUS has been published[16] and the study was prospectively registered on 9 August 2019 in the ISRCTN Registry (reference: ISRCTN69985145). THESEUS was a UK multicentre prospective non-randomised observational cohort study. The following five interventions were offered: (i) oral doxycycline 200mg once daily; (ii) oral clindamycin and rifampicin both 300mg twice daily for 10 weeks initially; (iii) laser treatment targeting the hair follicle (Nd-YAG, Diode or Alexandrite); (iv) deroofing, and (v) conventional surgery with the procedure and closure method determined by the operating surgeon.

Recruitment was achieved via a network of 10 hospitals spread across the UK, six sites being dermatology-led, two plastic surgery-led, and two already had a HS multidisciplinary team (MDT) approach integrating medical and surgical HS care. Sites were required to offer at least four of the five THESEUS interventions and were purposively selected to help balance recruitment into each intervention arm.

In this non-randomised study, the final intervention choice was based on participant preference for each of the interventions, combined with clinician-assessed eligibility, the shared decision-making process designed to replicate regular clinical practice. Participant preference was supported by a decision grid which described each intervention and provided the potential benefits and adverse effects in a head-to-head comparison (table S1). A video was also produced giving participants details of the deroofing intervention (https://www.youtube.com/watch?v=ftizgrBMzok&t=190s). Participants were asked to remain on their chosen intervention for the first six months, unless another treatment was medically indicated, after which they could switch intervention if they wished.

Except for the final few recruits, 12 months of follow up was undertaken, with study visits every three months, mirroring routine care. At baseline, participant demographics and previous HS medical and surgical treatment were recorded. Clinical examination at each review established the Hurley and refined Hurley stage defining baseline mild, moderate, and severe disease,[17] and lesion counts were performed to demonstrate changes in disease severity via the IHS4 instrument[18] and HiSCR trial endpoint.[19] Questionnaires were also administered to measure all six of the core domains recommended by the HIdradenitis SuppuraTiva cORe outcomes set International Collaboration (HISTORIC).[20] These included pain numerical rating scale (NRS), HS quality of life questionnaire (HiSQOL),[21] Patient Global Assessment,[22] number of patient-reported HS flares, the use of dressings, and fatigue.[23] Dermatology life quality index (DLQI)[24] and general health-related quality of life (EQ5D-5L) questionnaires were also administered. In addition, a text message was sent to consenting participants every day for 12 weeks, beginning on the day the intervention commenced, recording pain NRS.

As a pragmatic study, inclusion and exclusion criteria were designed to allow most secondary care HS patients to participate if they wished. Inclusion criteria were: (i) HS defined as a lifetime history of at

least five flexural skin boils or two in the last six months, confirmed on examination by a clinician with HS experience; (ii) at least 18 years old with active HS despite current treatment, and (iii) any stage of disease severity provided at least one of the THESEUS interventions was suitable. Exclusion criteria were: (i) unable or unwilling to provide written informed consent; (ii) pregnancy or breast feeding, and (iii) unable to complete outcome questionnaires in English. Participants could continue their current medical treatment on entry to the study, provided it was compatible with their chosen THESEUS intervention. Laser therapy was avoided in those taking oral tetracyclines due to the potential for photosensitivity. There were no restrictions on analgesia during the study.

Primary and secondary outcomes

The primary outcome of THESEUS was the proportion of participants who were eligible and hypothetically willing to receive the study interventions. Secondary outcomes were: (i) proportion selecting each intervention as their final choice with underpinning reasons; (ii) proportion of participants switching treatments, with reasons; (iii) treatment fidelity (concordance); (iv) loss to follow-up over 12 months, and (v) determination of OMI responsiveness based on outcomes after six months.

In keeping with an observational study, investigators recorded any adverse effects of THESEUS interventions at the time of scheduled follow up visits. Usual processes were followed for managing adverse effects, including UK yellow card reporting if needed. Characterisation of procedures was achieved by operators completing a report form in each case.

Sample size and statistical analysis

Reporting of this study is in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline (Table S1). The required sample size was 150 participants, allowing the proportion of participants hypothetically willing and eligible to be randomised in a clinical study to be estimated within a 95% confidence interval of ±7%. The pre-study surveys confirmed that the sample size should ensure recruitment of at least 20 participants for each intervention, sufficient to explore delivery in an IDEAL 2b evaluation, which provides a framework for the introduction of a novel surgical intervention.[25] THESEUS was not powered to test the relative efficacy of interventions and in most cases the analysis was limited to descriptive statistics (frequencies and percentages, mean and standard deviation, median and interquartile range). Statistical analysis was performed in Stata, StataCorp 2021 Stata Statistical Software: Release 17, College Station, TX: StataCorp LLC. The analysis was based on the participants' final treatment selection.

Patient and Public Involvement

Patient research partners (PRPs) were integral to the design and delivery of THESEUS. Three leaders of the HS Trust patient advocacy organisation were members of the Study Management Group and Study Steering Committee. THESEUS PRPs recommended creation of the decision grid (table S2) and selected the timing of the daily text messages at 6pm, responses being valid until 2am. Our PRPs also advised on Covid-19 pandemic mitigation strategies, including flexible remote follow up where necessary.

Results

Participant recruitment commenced in February 2020 and the target of 150 participants was reached in July 2021 (see Figure 1 for CONSORT study flow diagram). , There were two pauses in recruitment reflecting two waves of the Covid-19 pandemic in the UK in the Spring and Winter of 2020 (Figure 2). Overall, 291 patients were screened, of whom 149 (51%) were recruited; reasons for ineligibility and numbers who were eligible but declined are in table S3. Follow up rates were 89% (n=132), 83% (n=123, 70% (n=104) and 44% (n=65) at three, six, nine and 12 months respectively (Figure 1). The 12-month follow up rate was affected by pandemic-induced recruitment delays, which prevented 23 participants reaching the final follow up before THESEUS was closed to adhere to pre-specified study timelines. There were 17 study withdrawals, two from the doxycycline arm, three from clindamycin and rifampicin, eight from laser, one from deroofing and three from conventional surgery.

Baseline demographics of study participants are in table 1. Average age was 36 years (SD=10.5), 81% (n=121) were female, 20% (n=30) had non-white ethnicity, 86% had an elevated BMI (≥25.0), and 64% (n=95) were current or ex-smokers. Just over two-thirds of participants (69%, n=102) were Hurley stage II (moderate) at baseline, 13% (n=19) were stage I (mild), and 19% (n=28) were stage III (severe) (Table 2). Recent interventions received prior to study entry are in Table S4; 26% of participants received oral tetracyclines in the previous month and only 6% received adalimumab in the previous 3 months. Two-thirds (65%, n=95) of participants had received recent care from a dermatologist, 30% (n=45) from a surgeon, and 20% (n=29) from the Emergency Department (A&E) (Table 2).

Laser was the most popular intervention from a participant's perspective, with 41% (n=52) ranking it their most preferred option (Table 3). The THESEUS primary outcome of participant willingness and clinician-assessed eligibility to receive treatment was highest for laser (69%, n=102), followed by deroofing (58%, n=86), conventional surgery (54%, n=80), clindamycin and rifampicin (44%, n=65), and then doxycycline (37%, n=55) (Table 4) and this was mirrored by final intervention choice (Table 5).

Characterisation of ineligibility to receive the THESEUS interventions demonstrated that those with migratory skin lesions and absence of skin tunnels were less suited to deroofing or conventional surgery (Table S5). Participants with mild disease were more willing to receive the antibiotic interventions, while those with moderate-to-severe disease favoured non-antibiotic options (Table S6). Participant reported reasons for final intervention choice were dominated by 'My doctor recommended it', followed by 'I wanted to try something new' (Table 5), as confirmed by a nested qualitative interview study.[26]

Treatment concordance is summarised in tables S7(a) to (e). Of the 23 participants who chose doxycycline, concordance (in receipt of treatment) was 52% (n=12) after three months, and then 57% (n=13), 26% (n=6), and 17% (n=4) after six, nine, and 12 months respectively. Concordance with clindamycin and rifampicin was lower (30%, n=7/23) at three months, as participants had likely completed the initial 10-week course of treatment. Fidelity for the non-antibiotic interventions was substantially affected by delays in commencing treatment, due to a combination of THESEUS not mandating the timing of treatment as a non-randomised observational study, compounded by pandemic-induced delays. Only 43% (n=24) of the 56 participants choosing laser and one quarter (n=9) of the 35 participants selecting deroofing had started treatment at the 3-month review.

Efficacy data for each intervention during the twelve months of follow up are presented in table S8. In the doxycycline arm after three months there were modest reductions in HS severity (IHS4 score from 7

to 6), health related quality of life (HiSQOL score from 26.5 to 11.5 points, DLQI score from 6 to 3.5), and pain (pain NRS from 2 to 1). The small effect size may reflect relatively low baseline disease severity in this group. In the clindamycin and rifampicin arm, score reductions after three months were from 11 to 5 points for IHS4, 34 to 23 points for HiSQOL, 14 to 10.5 for DLQI, and from 4 to 2 for pain NRS. Interpretation of efficacy data for the non-antibiotic interventions is limited by the variable timing of intervention delivery across the 12 months of follow up. There were no serious adverse events and a total of 37 adverse effects were recorded from 29 participants (table S8), the commonest being gastrointestinal effects of the antibiotic interventions which led to treatment discontinuation in 8 participants in the doxycycline arm (35%) and 9 participants on rifampicin and clindamycin (39%). Laser and deroofing were both well-tolerated interventions.

In characterising the laser intervention, there were 196 procedures involving 56 participants. Four initial treatments one month apart were recommended and this was reflected by four being the mode of the number of treatments received (Figure 3), with a range from one to nine. Alexandrite was the commonest laser modality (44%), followed by ND:YAG (14%). In addition, 36% were intense pulsed light (IPL) treatment, which was not specified in the study protocol.[16] A total of 41 deroofing procedures were performed for 30 participants, 49% in the axilla and 32% in the groin. There was variation in the instrument used for incision, with needle tip diathermy used more often than loop diathermy. Identification of skin tunnels by blunt probing and secondary intention healing of the wound were highly conserved and performed for nearly all procedures. Low uptake of conventional surgery, due to lower participant preference and pandemic-related delays, meant there were insufficient procedures to characterise this intervention.

Discussion

THESEUS was a non-randomised, prospective observational cohort study designed to lay the foundations for future RCTs for HS. A spectrum of five medical, laser and surgical interventions, in addition to the relatively broad eligibility criteria, ensured THESEUS was as inclusive as possible, reflected by recruitment of 51% of secondary care patients screened. The study successfully introduced laser treatment targeting the hair follicle and deroofing to the UK, which previously were rarely offered, providing training and equipment for 10 centres spread across the country. The up-skilled centres are well placed to act as training hubs for their regions and to participate in future HS trials involving laser or deroofing.

Participant willingness and clinician-assessed eligibility for each intervention, the primary outcome of THESEUS, was greatest for laser treatment (69% of participants), followed by deroofing (58%), conventional surgery (54%), combined oral clindamycin and rifampicin (44%), and then oral doxycycline (37%). Final intervention choice was lower for conventional surgery than might be expected, probably reflecting the popularity of deroofing and pandemic-associated delays linked to reduced operating theatre access for surgical procedures requiring a general anaesthetic. Support for deroofing as an intervention is further indicated by the THESEUS deroofing information video (https://www.youtube.com/watch?v=ftizgrBMzok&t=190s) receiving more than one million views so far.

Doxycycline and other tetracyclines remain standard first line oral therapy for HS and could be a comparator arm in future RCTs, while being mindful of the relatively high treatment discontinuation rate in THESEUS. It should be noted that RCT evidence is currently limited to a single small trial comparing oral tetracycline with topical clindamycin from more than 20 years ago, using OMIs that have now been superseded.[27] THESEUS used doxycycline 200mg daily, twice the standard dose for acne and in line with treatment for other inflammatory skin conditions.[28] Combined oral clindamycin and rifampicin is a standard treatment recommended by several HS guidelines,[5,6,29] while lacking RCT evidence. Another prospective cohort study of 103 participants found similar results to THESEUS, with a reduction in median IHS4 score from 13 to 6, and a treatment discontinuation rate due to adverse effects of 16%, compared to 22% in THESEUS.[30]

Strengths of THESEUS include the 12 months of follow up, providing prospective data that is greatly needed in HS. Disease progression was relatively static during follow up, with the proportion of participants with Hurley stage III severe disease stable at 19%, 16%, and 21% across the baseline, 6-month, and 12-month reviews respectively. The baseline demographics of THESEUS participants, including two-thirds having moderate disease at baseline, are aligned with other studies[31] and THESEUS included slightly more non-white participants than the overall UK population.

Limitations of THESEUS include unexpected variation in the laser intervention, with one third of the procedures using IPL instead of laser. Nevertheless, several trials have found benefit of IPL in HS[32] and the mechanism of action, targeting the hair follicle, is very similar. Inclusion of IPL as well as laser treatment targeting the hair follicle in future RCTs for HS will depend on access to each modality and whether the trial is located towards the pragmatic or explanatory ends of the RCT spectrum. Delays encountered in provision of the non-medical interventions mean that interpretation of efficacy data is limited, however THESEUS was not powered to provide robust comparative effectiveness results. Another limitation is that only one treatment video was produced, which could have made deroofing more popular, however some participants chose not to receive deroofing after viewing the video. In addition, while retention rates were quite high for the first six months of the study, attrition was a factor at the nine and 12-month assessment points.

In conclusion, participant willingness and clinician-assessed eligibility for the five THESEUS interventions was greatest for laser and deroofing and THESEUS has introduced both interventions for HS to the UK. Further THESEUS details are provided in the HTA funding report[33] and in publications covering results from a nested process evaluation including participant interviews,[26] the feasibility of collecting daily pain NRS scores via text message,[14] and the outcomes from the THESEUS end-of-study workshop proposing future RCT designs.[15]

Acknowledgements

Thank you to all the THESEUS participants. The Centre for Trials Research is funded by Health & Care Research Wales and Cancer Research UK. We would also like to acknowledge the UK Dermatology Clinical Trials Network (UKDCTN) for their support for THESEUS.

References

1. Garg A, Neuren E, Cha D, et al. Evaluating patients' unmet needs in hidradenitis suppurativa: Results from the Global Survey Of Impact and Healthcare Needs (VOICE) Project. J Am Acad Dermatol 2020; 82: 366-76.

2. Frew JW, Lowes MA, Goldfarb N, et al. Global Harmonization of Morphological Definitions in Hidradenitis Suppurativa for a Proposed Glossary. JAMA Dermatology 2021; 157: 449-455.

3. Bechara FG, Podda M, Prens EP, et al. Efficacy and Safety of Adalimumab in Conjunction with Surgery in Moderate to Severe Hidradenitis Suppurativa: The SHARPS Randomized Clinical Trial. JAMA Surgery 2021; 156: 1001-9.

4. Ingram JR. Interventions for hidradenitis suppurativa updated summary of an original cochrane review. JAMA Dermatology 2017; 153: 458-9.

5. Ingram JR, Collier F, Brown D, et al. British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. Br J Dermatol 2019; 180: 1009-17.

6. Zouboulis CC, Desai N, Emtestam L, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol 2015; 29: 619-44.

7. Ingram JR, Abbott R, Ghazavi M, et al. The hidradenitis suppurativa priority setting partnership. Br J Dermatol 2014; 171: 1422-7.

8. Tierney E, Mahmoud BH, Hexsel C, et al. Randomized control trial for the treatment of hidradenitis suppurativa with a neodymium-doped yttrium aluminium garnet laser. Dermatologic Surgery 2009; 35: 1188-98.

9. Naouri M, Maruani A, Lagrange S, et al. Treatment of hidradenitis suppurativa using a long-pulsed hair removal neodymium:yttrium-aluminium-garnet laser: A multicenter, prospective, randomized, intraindividual, comparative trial. J Am Acad Dermatol 2021; 84: 203-5.

10. Van Der Zee HH, Prens EP, Boer J. Deroofing: A tissue-saving surgical technique for the treatment of mild to moderate hidradenitis suppurativa lesions. J Am Acad Dermatol 2010; 63: 475-80.

11. Hasan SB, Ingram JR. What has changed in the UK management of hidradenitis suppurativa from 2014 to 2019? Br J Dermatol 2020; 183: 973-5.

12. Howes R, Ingram JR, Thomas KS, et al. The surgical management of hidradenitis suppurativa in the United Kingdom: a national survey of care pathways informing the THESEUS study. J Plast Reconstr Aesthet Surg 2022; 75: 240-7.

13. Collier F, Howes R, Rodrigues J, et al. Primary care management of hidradenitis suppurativa: A cross-sectional survey of UK GPs. BJGP Open 2021; 5: 1-8.

14. Hasan S, et al. Feasibility of daily pain measurement using text messages in hidradenitis suppurativa clinical trials: data from THESEUS study. 2023 Submitted.

15. Leighton P, Howells L, Bates J, et al. Research Priorities in the Management of Hidradenitis Suppurativa. Br J Dermatiol 2023; doi: 10.1093/bjd/ljad152. Online ahead of print..

16. Bates J, Stanton H, Cannings-John R, et al. Treatment of Hidradenitis Suppurativa Evaluation Study (THESEUS): protocol for a prospective cohort study. BMJ Open 2022; 12: e060815.

17. Horvath B, Janse IC, Blok JL, et al. Hurley staging refined: A proposal by the dutch hidradenitis suppurativa expert group. Acta Derm Venereol 2017; 97: 412-3.

18. Zouboulis CC, Tzellos T, Kyrgidis A, et al. Development and validation of the International Hidradenitis Suppurativa Severity Score System (IHS4), a novel dynamic scoring system to assess HS severity. Br J Dermatol 2017; 177: 1401-9.

19. Kimball AB, Jemec GBE, Yang M, et al. Assessing the validity, responsiveness and meaningfulness of the Hidradenitis Suppurativa Clinical Response (HiSCR) as the clinical endpoint for hidradenitis suppurativa treatment. Br J Dermatol 2014; 171: 1434-42.

20. Thorlacius L, Ingram JR, Villumsen B, et al. A core domain set for hidradenitis suppurativa trial outcomes: an international Delphi process. Br J Dermatol 2018; 179: 642-50.

21. Kirby JS, Thorlacius L, Villumsen B, et al. The Hidradenitis Suppurativa Quality of Life (HiSQOL) score: development and validation of a measure for clinical trials. Br J Dermatol 2020; 183: 340-8.

22. Kirby JS, Hereford B, Thorlacius L, et al. Validation of global item for assessing impact on quality of life of patients with hidradenitis suppurativa*. Br J Dermatol 2021; 184: 681-7.

23. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. Arch Neurol 1989; 46: 1121-3.

24. Finlay AY, Khan GK. Dermatology Life Quality Index (DLQI) - A simple practical measure for routine clinical use. Clin Exp Dermatol 1994; 19: 210-6.

25. Pennell CP, Hirst AD, Campbell WB, et al. Practical guide to the Idea, Development and Exploration stages of the IDEAL Framework and Recommendations. Br J Surg 2016; 103: 607-15.

26. Howells L, Leighton P, Thomas KS, et al. "I'll try anything, but I do not want the same tablets again": a qualitative interview study exploring patient views and experiences of treatment for Hidradenitis Suppurativa in the UK. 2023 (Submitted).

27. Jemec GBE, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. J Am Acad Dermatol 1998; 39: 971-4.

28. Williams HC, Wojnarowska F, Kirtschig G, et al. Doxycycline versus prednisolone as an initial treatment strategy for bullous pemphigoid: a pragmatic, non-inferiority, randomised controlled trial. Lancet 2017; 389: 1630-8.

29. Alikhan A, Sayed C, Alavi A, et al. North American clinical management guidelines for hidradenitis suppurativa: A publication from the United States and Canadian Hidradenitis Suppurativa Foundations: Part II: Topical, intralesional, and systemic medical management. J Am Acad Dermatol 2019; 81: 91-101.

30. van Straalen KR, Tzellos T, Guillem P, et al. The efficacy and tolerability of tetracyclines and clindamycin plus rifampicin for the treatment of hidradenitis suppurativa: Results of a prospective European cohort study. J Am Acad Dermatol 2021; 85: 369-78.

31. Kimball AB, Okun MM, Williams DA, et al. Two phase 3 trials of adalimumab for hidradenitis suppurativa. N Engl J Med. 2016; 375: 422-34.

32. Andersen P, Riis PT, Thorlacius L, et al. Intense pulsed light treatment for hidradenitis suppurativa: a within-person randomized controlled trial. Eur J Dermatol 2020; 30: 723-9.

33. Ingram JR, Bates J, Cannings-John R, et al. Treatment of Hidradenitis Suppurativa Evaluation Study (THESEUS): a prospective cohort study. Health technology assessment 2023 (submitted).

Figure legends

Figure 1. Flow diagram of screening, recruitment and participant attrition.

Figure 2. Cumulative recruitment influenced by Covid-19 pandemic.

Figure 3. Number of laser/ light treatments per participant.

Table 1

Baseline characteristics of participants

Demographics	**Descriptive statistics[a]**
Age (years) Mean (SD)	36.1 (10.5)
Female n (%)	121 (81.2)
Ethnic group or background n(%)	
White	118 (79.7)
Mixed/Multiple ethnic groups	8 (5.4)
Asian/Asian British	9 (6.1)
Black/African/Caribbean/Black British	11 (7.4)
Other ethnic background	2 (1.4)
Fitzpatrick scale n (%)	
I-Very fair; always burns, cannot tan	17 (11.5)
II-Fair; usually burns, sometimes tans	50 (33.8)
III-Medium; sometimes burns, usually tans	46 (31.1)
IV-Olive; rarely burns, always tans	13 (8.8)
V-Brown; rarely burns, tans easily	16 (10.8)
VI-Dark brown; never burns, always tans	6 (4.1)
Body Mass Index (BMI) (kg/m²)	N=143
BMI Mean (SD)	33.0 (7.9)
Healthy weight (BMI ≥18.5 to 24.9 kg/m2), n (%)	20 (14.0)
Overweight (BMI ≥25.0 to 29.9 kg/m2), n (%)	40 (28.0)
Obese (BMI ≥30.0 to 39.9 kg/m2), n (%)	54 (37.8)
Severely obese (BMI ≥40 kg/m2), n (%)	29 (20.3)

Demographics	Descriptive statistics[a]
Index of Multiple Deprivation (IMD) quintiles n (%)	
1-Least deprived	15 (10.1)
2--	29 (19.5)
3---	31 (20.8)
4----	37 (24.8)
5-----Most deprived	37 (24.8)
Type of study site n (%)	
Dermatology-led (6 sites)	64 (43.0)
Surgery-led (2 sites)	50 (33.5)
Pre-established multidisciplinary service (2 sites)	35 (23.5)
Smoking n (%)	
Non smoker	53 (35.8)
Ex-smoker	32 (21.6)
Current smoker	63 (42.6)
For smokers, number cigarettes smoked per day, Median (IQR)	*10.0 (5.0 to 11.0)*
Nicotine replacement therapy n (%)	21 (14.3)

Overall n=149. Index of Multiple Deprivation is a standard dataset used in the UK to classify the relative affluence or poverty of small geographical areas. SD=standard deviation; IQR= interquartile range. Detail of missing or not applicable observations: n=1 sex, n=1 ethnicity, n=6 BMI, n=1 Smoking

Table 2

Baseline HS severity and specialty providing HS care

Baseline variables	Descriptive statistics[a]
Clinical history	
Participants' HS recently treated by: n (%)	
General Practitioner (GP)	103 (70.1)
Dermatologist	95 (64.6)
Surgeon	45 (30.6)
Doctor in Accident & Emergency	29 (19.7)
Nurse (community/primary care)	29 (19.7)
Anybody else (others)	12 (8.1)
Severity of HS	
Skin region affected: n (%)	
Axilla	102 (68.5)
Groin	114 (76.5)
Perineum	47 (31.8)
Buttocks	58 (38.9)

Baseline variables	Descriptive statistics[a]
Chest	46 (30.9)
Other	45 (30.4)
Total number of inflammatory nodules Median (IQR)	4 (1.0 to 8.5)
Total number of abscesses Median (IQR)	1 (0 to 3)
Total number of draining or inflamed skin tunnels Median (IQR)	1 (0 to 2)
International Hidradenitis Suppurativa Severity Score System (IHS4)[a] Median (IQR)	11 (4 to 21)
Number of HS flares in the last month Median (IQR)	4 (2 to 10)
Drainage of pus, blood, other fluid due to HS[b] Median (IQR)	3.5 (0 to 6)
Magnitude of skin odour[b] Median (IQR)	3.5 (0 to 7)
Hurley stage (most severely affected region) n (%)	
H-I: Mild; individual, non-scarring lesions	19 (12.8)
H-II: Moderate; multiple scarring lesions separated by normal skin	102 (68.5)
H-III: Severe; lesions coalescing into inflammatory plaques	28 (18.8)
Skin lesions fixed in location or migratory n (%)	
Fixed	94 (63.5)
Migratory	54 (36.5)
Draining skin tunnels due to HS present in any skin region n (%)	86 (58.1)
3 or more body regions with draining skin tunnels n (%)	27 (18.1)
Skin regions across body with at least 1% interconnected draining tunnels n (%)	15 (10.1)
Refined Hurley stage for HS severity n (%)	
Hurley IA	13 (8.7)
Hurley IB	32 (21.5)
Hurley IC	18 (12.1)
Hurley IIA	12 (8.1)
Hurley IIB	14 (9.4)
Hurley IIC	45 (30.2)
Hurley III	15 (10.1)
How was lesion count assessed for the purposes of this review n (%)	
By a health professional in person	47 (69.1)
By the patient self-reported	21 (30.9)

Overall n=149. SD=standard deviation; IQR= interquartile range.

[a] IHS4 score is calculated by the number of inflammatory nodules plus the number of abscesses (multiplied by 2) plus the number of draining tunnels (multiplied by 4). Higher score indicates more severe disease. [b] Scored from 0-10 where 0 is none and 10 is worst imaginable.

Table 3

Participant willingness and clinician assessed eligibility for THESEUS interventions (N=149)

	Doxycycline		Clindamycin & rifampicin		Laser		Deroofing		Conventional surgery	
	N	**%**	**n**	**%**	**n**	**%**	**n**	**%**	**n**	**%**
Willingness										
Participant willing to receive treatment	63	(42.3)	76	(51.0)	118	(79.2)	99	(66.4)	95	(64.2)
Reasons for ngness:										
Will not provide enough benefit	14	(9.4)	12	(8.1)	18	(12.1)	23	(15.5)	19	(12.8)
Potential side effects/complications	11	(7.4)	12	(8.1)	1	(0.7)	5	(3.4)	13	(8.8)
Had this before - not effective	40	(26.8)	29	(19.5)	1	(0.7)	4	(2.7)	3	(2.0)
Had this before - experienced side effects	15	(10.1)	14	(9.4)	1	(0.7)	0	(0.0)	0	(0.0)
Information from other sources	0	(0.0)	0	(0.0)	1	(0.7)	1	(0.7)	2	(1.4)
Other reason	6	(4.0)	6	(4.0)	9	(6.0)	17	(11.5)	16	(10.8)
Patient Ranked 1 (most preferred)	17	(14.3)	19	(15.8)	52	(40.6)	26	(20.8)	15	(12.0)
Clinician assessed eligibility										
Clinically appropriate	88	(59.5)	96	(64.9)	89	(59.7)	100	(67.1)	94	(63.1)
Eligible but treatment not available at the site	na		na		22	(14.8)	na		na	

na= not applicable

Table 4

Primary outcome: participant willingness and eligibility for THESEUS interventions

Primary outcome: patients willing and eligible for study intervention[a]	n	(%)
Doxycycline	55	(36.9)
Clindamycin & rifampicin	65	(43.6)
Laser	102	(68.5)
Deroofing	86	(57.7)
Conventional surgery	80	(53.7)

[a] Patients could be willing and eligible for more than one treatment; categories are not mutually exclusive

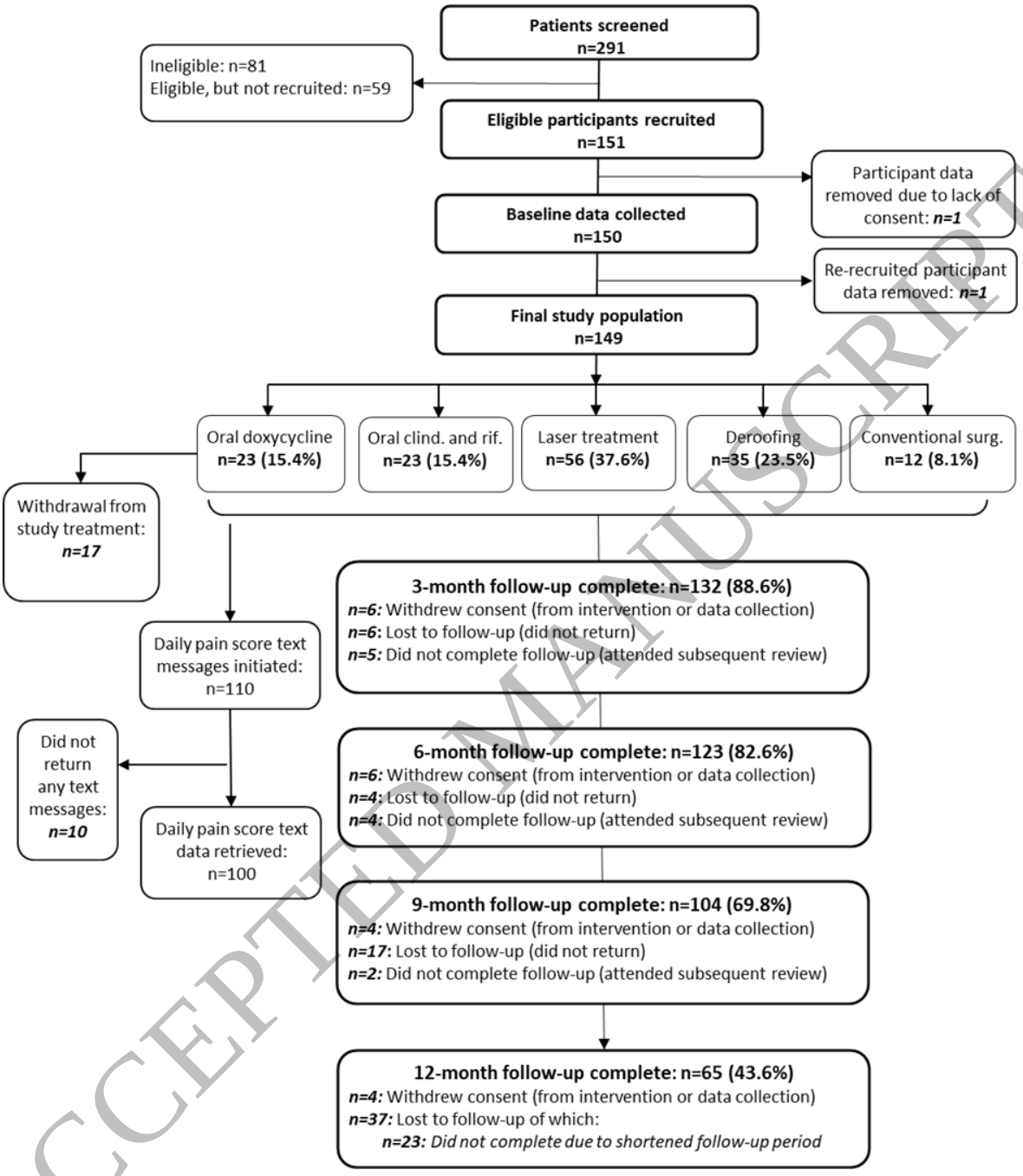
Table 5

Final intervention choice and participant reported reasons

	Final intervention choice[a]				
	Doxycycline	**Clindamycin & rifampicin**	**Laser**	**Deroofing**	**Conventional surgery**
n (%)	**23** (15.4)	**23** (15.4)	**56** (37.6)	**35** (23.5)	**12** (8.1)
Patients' ranking of treatment					
1 = most preferred	16 (70%)	19 (83%)	51 (91%)	25 (71%)	11 (92%)
2			1 (2%)	1 (3%)	
3	1 (4%)			1 (3%)	
4	1 (4%)	3 (13%)			
5 = least preferred					
Missing	5 (22%)	1 (4%)	4 (7%)	8 (23%)	1 (8%)
Reason for deciding on the final treatment:					
My doctor recommended it	15 (65.2)	15 (68.2)	27 (49.1)	27 (77.1)	3 (25.0)
I wanted to try something new	5 (21.7)	5 (22.7)	15 (27.3)	2 (5.7)	1 (8.3)
I've used it before	1 (4.4)	1 (4.6)	0	0	4 (33.3)
Based on:					
information read in THESEUS information sheet	2 (8.7)	0	5 (9.1)	2 (5.7)	0
information read on	0	0	1 (1.8)	1 (2.9)	2 (16.7)

website(s)					
information read in THESEUS decision grid	0	1 (4.6)	1 (1.8)	0	0
My preferred option was not available	0	0	1 (1.8)	1 (2.9)	0
Other reason	0	0	5 (9.1)	2 (5.7)	2 (16.7)

[a] Patients could only choose one intervention as their final choice. Missing n=2.



Oral clind. and rif. = Oral clindamycin and rifampicin

Figure 1

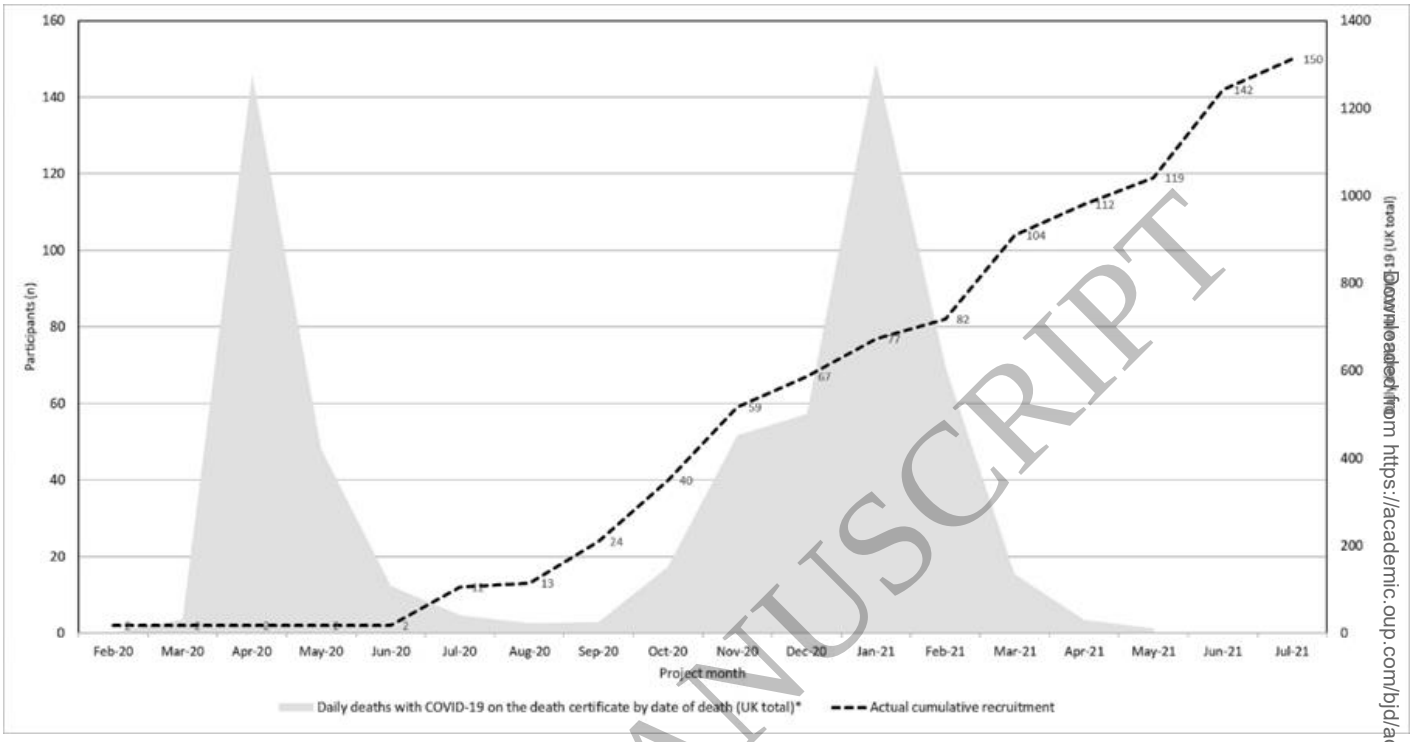


Figure 2

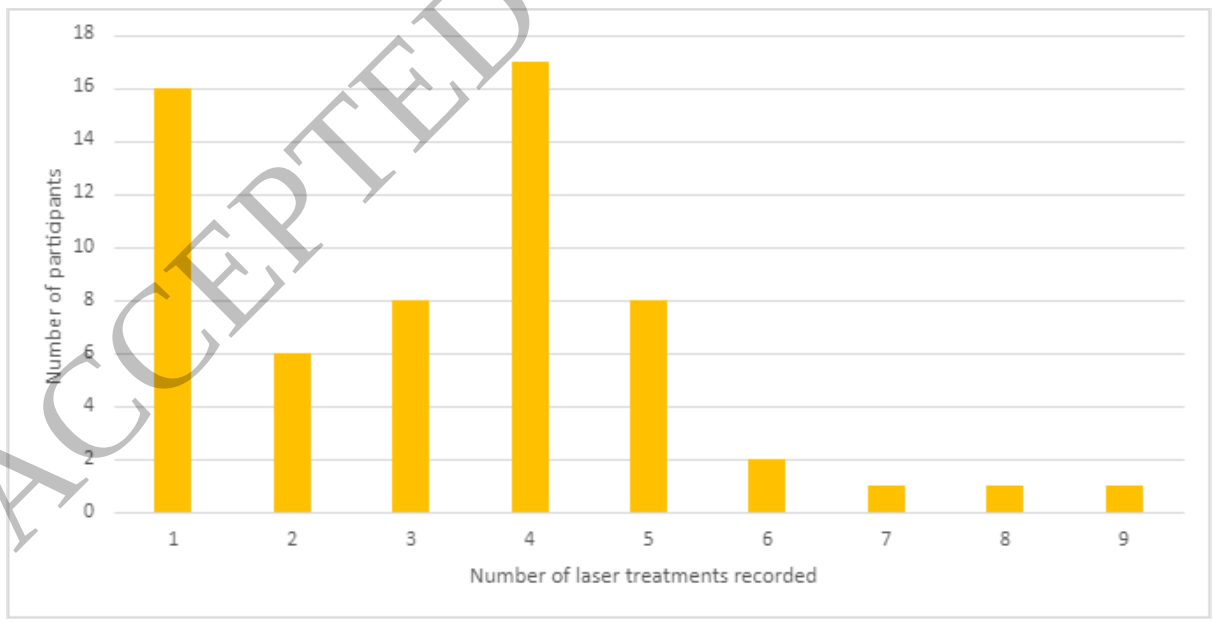


Figure 3

Bimzelx® ▼
(bimekizumab)

THIS ADVERT CONTAINS PROMOTIONAL CONTENT FROM UCB AND IS INTENDED FOR HCPS IN GREAT BRITAIN ONLY

THE OPPORTUNITY FOR COMPLETE, FAST AND LASTING SKIN CLEARANCE [1,2]

68.2% achieved PASI 100 at Week 16[¥1]
75.9% of patients achieved PASI 75 at Week 4[¥1]
82% of week 16 PASI 100 responders maintained this response up to 3 years[2]

BIMZELX was well tolerated, the most frequently reported adverse reactions were: upper respiratory tract infections (14.5%, 14.6%, in plaque psoriasis (Pso), and psoriatic arthritis (PsA) respectively) and oral candidiasis (7.3%, 2.3% in Pso, and PsA respectively). Other common reported adverse reactions include Tinea infections, Ear infections, Herpes simplex infections, Oropharyngeal candidiasis, Gastroenteritis, Folliculitis, Headache, Rash, Dermatitis, Eczema, Acne, Injection site reactions, and Fatigue.
Please refer to the SmPC for further information.[1]

Challenge expectations in plaque psoriasis[1,2]

Visit **Bimzelx.co.uk** to discover more.

This site contains promotional information on UCB products.

Stay connected with UCB by scanning the QR code and set your digital preferences.

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This is a promotional UCB website

Footnotes: ¥co-primary endpoints PASI 90 and IGA 0/1 at Week 16
Pso - Plaque Psoriais; PsA - Psoriatic Athritis

BIMZELX® (Bimekizumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Bimzelx, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Please refer to the SmPC for further information.[1]

PRESCRIBING INFORMATION FOR HCP'S IN GREAT BRITAIN

BIMZELX® ▼ (Bimekizumab) is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy; and for active psoriasis arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs), alone or in combination with methotrexate.[1] (Please consult the Summary of Product Characteristics (SmPC) before prescribing).

Active Ingredient: Bimekizumab – solution for injection in pre-filled syringe or pre-filled pen: *160 mg of bimekizumab in 1 mL of solution (160mg/mL)*. **Indications:** Moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. Alone or in combination with methotrexate, for active psoriatic arthritis in adults who have had an inadequate response or intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to non-steroidal anti-inflammatory drugs (NSAIDs). Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy. **Dosage and Administration:** Should be initiated and supervised by a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated. **Recommended dose:** Plaque Psoriasis: 320 mg (given as two subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. Psoriatic arthritis: 160 mg (given as 1 subcutaneous injection of 160 mg) every 4 weeks. For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, the recommended dose is the same as for plaque psoriasis. After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160 mg every 4 weeks can be considered. Axial spondyloarthritis (nr-axSpA and AS): 160 mg (given as 1 subcutaneous injection) every 4 weeks. For patients with plaque psoriasis (including psoriatic arthritis with coexistent moderate to severe psoriasis) and a body weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response. Consider discontinuing if no improvement by 16 weeks of treatment. Renal or hepatic impairment: No dose adjustment needed. Elderly: No dose adjustment needed. Administer by subcutaneous injection to thigh, abdomen or upper arm. Rotate injection sites and do not inject into psoriatic plaques or skin that is tender, bruised, erythematous or indurated. Do not shake pre-filled syringe or pre-filled pen. Patients may be trained to self-inject. **Contraindications:** Hypersensitivity to bimekizumab or any excipient; Clinically important active infections (e.g. active tuberculosis). **Warnings and Precautions:** Record name and batch number of administered product. *Infection:* Bimekizumab may increase the risk of infections e.g. upper respiratory tract infections, oral candidiasis. Caution when considering use in patients with a chronic infection or a history of recurrent infection. Must not be initiated if any clinically important active infection until infection resolves or is adequately treated. Advise patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops an infection, the patient should be carefully monitored. If the infection becomes serious or is not responding to standard therapy do not administer bimekizumab until infection resolves. *TB:* Evaluate for TB infection prior to initiating bimekizumab – do not give if active TB. While on bimekizumab, monitor for signs and symptoms of active TB. Consider anti-TB therapy prior to bimekizumab initiation if past history of latent or active TB in whom adequate treatment course cannot be confirmed. *Inflammatory bowel disease:* Bimekizumab is not recommended in patients with inflammatory bowel disease. Cases of new or exacerbations of inflammatory bowel disease have been reported. If inflammatory bowel disease signs/symptoms develop or patient experiences exacerbation of pre-existing inflammatory bowel disease, discontinue bimekizumab and initiate medical management. *Hypersensitivity:* Serious hypersensitivity reactions including anaphylactic reactions have been observed with IL-17 inhibitors. If a serious hypersensitivity reaction occurs, discontinue immediately and treat. *Vaccinations:* Complete all age appropriate immunisations prior to bimekizumab initiation. Do not give live vaccines to bimekizumab patients. Patients may receive inactivated or non-live vaccinations. **Interactions:** A clinically relevant effect on CYP450 substrates with a narrow therapeutic index in which the dose is individually adjusted e.g. warfarin, cannot be excluded. Therapeutic monitoring should be considered. **Fertility, pregnancy and lactation:** Women of child-bearing potential should use an effective method of contraception during treatment and for at least 17 weeks after treatment. Avoid use of bimekizumab during pregnancy. It is unknown whether bimekizumab is excreted in human milk, hence a risk to the newborn/infant cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Bimzelx therapy. No data available on human fertility. **Driving and use of machines:** No or negligible influence on ability to drive and use machines. **Adverse Effects:** Refer to SmPC for full information. Very Common *(≥ 1/10):* upper respiratory tract infection; Common *(≥ 1/100 to < 1/10):* oral candidiasis, tinea infections, ear infections, herpes simplex infections, oropharyngeal candidiasis, gastroenteritis, folliculitis; headache, rash, dermatitis and eczema, acne, injection site reactions, fatigue; Uncommon *(≥ 1/1,000 to < 1/100):* mucosal and cutaneous candidiasis (including oesophageal candidiasis), conjunctivitis, neutropenia, inflammatory bowel disease. Storage precautions: Store in a refrigerator (2°C – 8°C), do not freeze. Keep in outer carton to protect from light. Bimzelx can be kept at up to 25°C for a single period of maximum 25 days with protection from light. Product should be discarded after this period or by the expiry date, whichever occurs first.

Legal Category: POM
Marketing Authorisation Numbers: PLGB 00039/0802 (Pre-filled Syringe), PLGB 00039/0803 (Pre-filled Pen).
UK NHS Costs: £2,443 per pack of 2 pre-filled syringes or pens of 160 mg each.
Marketing Authorisation Holder: UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE, United Kingdom.
Further information is available from: UCB Pharma Ltd, 208 Bath Road, Slough, Berkshire, SL1 3WE. Tel: 0800 2793177 Email: ucbcares.uk@ucb.com
Date of Revision: August 2023 (GB-P-BK-AS-2300047)
Bimzelx is a registered trademark.

Adverse events should be reported. Reporting forms and information can be found at http://www.mhra.gov.uk/yellowcard. Adverse events should also be reported to UCB Pharma Ltd at ucbcares.uk@ucb.com or 0800 2793177.

References: 1. BIMZELX (bimekizumab) SmPC. Available at: https://www.medicines.org.uk/emc/product/12834/smpc. Accessed September 2023 **2.** Strober et al. [BE BRIGHT open label extension] Br J Dermatol. 2023. 188(6): 749-759.

GB-BK-2300081 Date of preparation: September 2023.

Inspired by patients. Driven by science.

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