Skin irradiation using intense pulsed light and radiofrequency for Hurley Stage I or II hidradenitis suppurativa[1]

EXTRACT

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Intense Pulsed Light Therapy, Radiofrequency Therapy, Hidradenitis Suppurativa, Benefit Assessment, Systematic Review

The responsibility for the contents of the report lies solely with IQWiG.

According to §139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received". The Institute received the completed Form for disclosure of potential conflicts of interest from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Chapter A8 of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

External experts

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IQWiG thanks the external expert for his collaboration in the project.

Patient and family involvement

Five patients were consulted during the preparation of the report. Christian Loefs, Ingeborg Manderscheid-Feld, Kerstin Rosinski, Marko Schmidt and one further person participated in the discussion. The aim of the discussion was to obtain information on the following topics: The impact of the condition on life and daily activities and how people cope, treatment preferences including treatment goals, and experiences and concerns about treatment. IQWiG would like to thank the above participants for taking part in the discussion and the self-help group "Mullewupp e.V." for their support. Neither this group nor the participants were involved in the actual writing of the report.

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Key statement

Research question

The aim of this investigation is to assess the benefit of skin irradiation using a combination of intense pulsed light (IPL) and radiofrequency (RF) plus topical antibiotics (TABs) compared to TABs alone in patients with Hurley Stage I or II hidradenitis suppurativa (HS). This condition is also known as acne inversa, abbreviated to HS/AI below.

Conclusion

Data from a high-quality study provide an indication that, for patients with Stage I or II HS/AI, skin irradiation using a combination of IPL and RF plus TABs is more beneficial than TABs alone across all outcomes. This conclusion is particularly supported by the results for treatment response (disease severity), which showed substantially greater improvement in patients treated with the combination therapy. Any adverse events were temporary and not serious

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List of abbreviations

Abbreviation	Meaning
AE	adverse event
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HADS	Hospital Anxiety and Depression Scale
HTA	health technology assessment
HiSCR	Hidradenitis Suppurativa Clinical Response
HS/AI	hidradenitis suppurativa / acne inversa
IHS4 or IHS4-55	International Hidradenitis Suppurativa Severity Scoring System
IPL	intense pulsed light
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MD	mean difference
MMRM	Mixed Model for Repeated Measurements
NRS	Numeric Rating Scale
OR	odds ratio
RCT	randomized controlled trial
RF	radio frequency
SAE	serious adverse event
SAHS	Severity Assessment of Hidradenitis Suppurativa
SD	standard deviation
TAB	topical antibiotic

1 Background

Hidradenitis suppurativa, also known as acne inversa and abbreviated as HS/AI, is a chronic, recurrent inflammatory skin disease of the terminal sebaceous glands. The painful lesions, which can substantially impair quality of life, usually occur in the axillary, inguinal, and anogenital regions [1,2]. Although the aetiology of HS/AI has not been conclusively clarified, genetic predisposition appears to play a major role, among other factors [1]. Trigger factors include smoking and obesity. The diagnosis is primarily made clinically based on medical history and physical examination [1,2]. The global prevalence is between 1% and 4% [1].

In view of the severity of the inflammation, which is present at any time, the disease is classified into an active, inflammatory form and an inactive, predominantly non-inflammatory form. Numerous classification and severity assessment tools are available. The Hurley score from 1996 is historically established and is particularly suitable for documenting the decision to undergo radical surgical therapy (extensive resection) in patients with the inactive, predominantly non-inflammatory form. It divides HS/AI into 3 clinical stages [2]:

- Stage I: single abscesses, no fistula tracts and scarring
- Stage II: 1 or more widely separated abscesses with fistula tracts and scarring
- Stage III: extensive involvement with abscesses, fistula tracts, and scarring

However, the Hurley score is not dynamic and is therefore not suitable for documenting disease activity. In contrast, the International Hidradenitis Suppurativa Severity Scoring System (IHS4), for example, is suitable for classification into mild, moderate, and severe HS/AI, as well as for documenting disease activity and progression, especially in the active, inflammatory form [2,3]. Another tool often used in clinical studies is the Hidradenitis Suppurativa Clinical Response (HiSCR) score. A 50% improvement in severity is usually considered a successful outcome and is often used as a treatment goal [2,4].

Since the disease is incurable, treatments aim to improve symptoms. Depending on the severity of HS/AI and other patient-specific characteristics, the German S2k guideline recommends primarily drug or radical surgical treatments. Drug treatments include topical antibiotics (TABs) (clindamycin 1% solution), oral systemic antibiotics (doxycycline), hormonal antiandrogens (ethinyl oestradiol in combination with cyproterone acetate), and monoclonal antibodies (adalimumab, bimekizumab, or secukinumab). Radical surgery is indicated for inactive, predominantly non-inflammatory HS/AI with increasing severity and irreversible tissue damage [2]. The treatments listed above from the German S2k guideline are also largely mentioned in guidelines from other countries, such as Canada, the USA, and the United Kingdom [5,6]. Furthermore, device-based treatments are also available. For example, a combination of intense pulsed light (IPL) and radiofrequency (RF), also known as LAight

therapy, can be used in addition to TABs, particularly in the active, inflammatory form of HS/AI with mild to moderate severity [2].

2 Research question

The aim of this investigation is

- to assess the benefit of skin irradiation using a combination of IPL and RF plus TABs compared to TABs alone

in patients with Hurley Stage I or II hidradenitis suppurativa (HS). This condition is also known as acne inversa, abbreviated to HS/AI below.

3 Methods

The target population for the benefit assessment was patients with Hurley Stage I or II HS/AI. The test intervention was skin irradiation using a combination of IPL and RF plus TABs. The control intervention was TABs alone.

The following categories of patient-relevant outcomes were considered:

- Morbidity (e.g., surgical interventions, disease severity, pain, response to therapy)
- Health-related quality of life
- Adverse effects

Only randomized controlled trials (RCTs) were included in the benefit assessment. There were no restrictions on the duration of the studies.

A systematic literature search for studies was conducted in the MEDLINE, Embase, and Cochrane Central Register of Controlled Trials databases. At the same time, a search for relevant systematic reviews was conducted in MEDLINE, the Cochrane Database of Systematic Reviews, and the International Health Technology Assessment (HTA) Database, as well as on the websites of the National Institute for Health and Care Excellence (NICE) and the Agency for Healthcare Research and Quality (AHRQ).

In addition, the following sources of information and search techniques were considered: study registries, manufacturer inquiries, documents submitted by the Federal Joint Committee (G-BA), review of reference lists, and author inquiries.

The selection of relevant studies was carried out independently by 2 reviewers. Any discrepancies were resolved through discussion. Data extraction was performed in standardized tables. To assess the qualitative certainty of the results, cross-outcome and outcome-specific criteria for risk of bias were evaluated and the risk of bias was classified as low or high in each case. The results of the individual studies were described according to outcomes.

In addition to comparing the results of the individual studies, meta-analyses and sensitivity analyses were performed and effect modifiers were examined, provided that the methodological requirements were met.

For each outcome, a conclusion was drawn regarding the evidence for (greater) benefit and (greater) harm, with 4 levels of certainty of conclusions: proof (highest certainty of conclusions), indication (moderate certainty of conclusions), hint (lowest certainty of conclusions), or neither of the above 3. The latter was the case if no data were available or

the available data did not allow any of the other 3 conclusions to be drawn. In this case, the conclusion “There is no hint of (greater) benefit or (greater) harm” was drawn.

Subsequently, an assessment of benefit and harm was carried out across outcomes.

In cases where there is no hint of (greater) benefit or (greater) harm, a conclusion was drawn on the potential of the intervention in terms of a necessary treatment alternative, and corresponding key points of a testing study were formulated.

4 Results

4.1 Results of the information retrieval

The information retrieval yielded 1 RCT relevant to the research question (Table 1). No planned or ongoing studies were identified.

The search strategy for bibliographic databases and study registries are in the Appendix. The last search took place on 23 May 2024.

Table 1: Study pool of the benefit assessment

Study	Available documents			
	Full-text publication (in scientific journals)	**Registry entry / results report from study registries**	**Study from manufacturer documents (not publicly available)**	**Other documents**
RELIEVE	yes [7,8]	yes [9] / no	no	yes: study protocol [10]

4.2 Characteristics of the study included in the assessment

The 2-arm RELIEVE RCT [7,8], with study centres in Germany and Poland, included adult patients with Hurley Stage I or II HS/AI. In addition, patients had to have at least 3 inflammatory nodules or abscesses and at least 1 typical HS/AI location affected (axillary, inguinal, gluteal, mammary). Patients were excluded from participating in the study if they had Stage III HS/AI, had a contraindication for combined skin irradiation using IPL and RF[2] or for topical application of clindamycin (1% solution), or had already undergone treatment with combined skin irradiation using IPL and RF. In addition, all patients whose current treatment included oral antibiotics or who had been treated with a biologic in the past 6 months were excluded.

The RCT consisted of 2 phases (Periods A and B) of 16 weeks each, with a total duration of 32 weeks. Data collection was scheduled at baseline and after 8, 16, 24, and 32 weeks. In Period A, the intervention group was to receive treatment with topical clindamycin (1% solution) and 8 sessions of combined IPL and RF skin irradiation every 2 weeks during the first 16 weeks. The control group was treated exclusively with topical clindamycin (1% solution) during the same period. In Period B, which followed directly on from Period A, both groups were treated exclusively with combined IPL and RF skin irradiation (8 sessions) for a further 16 weeks. As

[2] Contraindications for combined skin irradiation using IPL and RF include pregnancy, epilepsy, electronically controlled implants (such as pacemakers/stimulators), extreme photosensitivity, melanoma or skin cancer, contagious skin diseases, tattoos, piercings, permanent makeup, or branding on the areas of the body to be treated, injections (within the last 6 months) in the areas of the body to be treated (e.g., Botox or hyaluronic acid), and implants within a 10 cm radius of the areas of the body to be treated [10].

only Period A is relevant for the present benefit assessment, Period B will not be discussed further, except for the data on adverse events (AEs), which were examined for additional findings.

Of the 88 patients included in the study, 45 were randomized to the intervention group and 43 to the control group. Data collection at the planned times was incomplete due to COVID-19 lockdowns. This affected 2 patients at baseline from the intervention group and 3 patients in Week 8 and 1 patient in Week 16 from the control group. Furthermore, 10 patients missed part of the planned treatments with combined IPL and RF skin irradiation as a result of pandemic measures. In 1 case, TABs were discontinued in the intervention group due to an AE. Using a mixed-effects model for repeated measures (MMRM), data from all patients with a baseline value and at least one additional value at an observation time (Week 8 and/or Week 16) were included in the analyses. Thus, after 16 weeks, data from up to 41 of the 45 (91%) patients in the intervention group and up to 40 of the 43 (93%) patients in the control group were included in the analyses.

4.3 Overview of patient-relevant outcomes

Data on patient-relevant outcomes were extracted from 1 study. Table 2 shows an overview of the available data on patient-relevant outcomes.

Table 2: Matrix of patient-relevant outcomes

Study	Outcomes								
	Morbidity				QoL	Adverse effects			
	Treatment response (disease severity)	Anxiety symptoms and depressive symptoms	Pain	Surgical interventions	Health-related quality of life	AEs	Discontinuations due to AEs	Severe AEs	SAEs
RELIEVE	●[a]	●[b]	●[c]	–	●[d]	●	○[e]	●[f]	●[f]

●: Data were reported and were usable.
○: Data were reported but were not usable for the benefit assessment.
–: The outcome was not measured.
a. Collected with IHS4-55.
b. Collected with HADS.
c. Collected with NRS.
d. Collected with DLQI.
e. No systematic collection and analysis.
f. No events occurred.

AE: adverse event¸ DLQI: Dermatology Life Quality Index; HADS: Hospital Anxiety and Depression Scale; IHS4-55: International Hidradenitis Suppurativa Severity Scoring System; NRS: Numeric Rating Scale; QoL: (health-related) quality of life; SAE: serious adverse event.

The relevant assessment tools are described below and the response criteria used are examined:

- For the outcome category of morbidity, data from 3 different operationalizations were available from only 1 study using the IHS4, IHS4-55, and HiSCR, which had the same data basis or a major overlap:
  - The IHS4, which is used in the literature to assess the severity of the disease, forms a total score based on the number of nodes, abscesses, and draining fistulas, which are weighted 1-, 2-, and 4-fold, respectively [3].
  - The IHS4-55, which is used in the literature to assess treatment response, aims to operationalize the IHS4 by classifying patients as responders or non-responders based on the IHS4 data. Patients with a reduction in the IHS4 total score of at least 55% are defined as responders [11].
  - Based on the HiSCR, which is also used in the literature to assess treatment response, patients are classified as responders and non-responders. Responders are defined as

patients with a reduction in inflammatory lesions (sum of abscesses and inflammatory nodules) of at least 50% who have not experienced an increase in the number of abscesses or draining fistulas compared to baseline [4,12].

All 3 instruments are valid and adequately operationalize the respective patient-relevant outcome. To address the problem of multiplicity, the IHS4-55 was used as the overarching instrument for the present assessment, as explained below: The analyses of the continuous data from the IHS4 do not allow for a direct relevance assessment, in contrast to the IHS4-55 and HiSCR, for which responder analyses with a suitable response criterion are available. Compared to the HiSCR, the IHS4-55 takes draining fistulas into account to a greater extent [11], so that, in view of the clinical picture, the IHS4-55 was considered more suitable for the present assessment and was therefore used. In the following, the outcome is referred to as "treatment response (disease severity)". When drawing a conclusion on the evidence base, it was checked whether the HiSCR data (not shown) were essentially consistent with those of the IHS4-55 and whether, in principle, the same evidence base would have been established.

- The Hospital Anxiety and Depression Scale (HADS) is a patient-reported instrument for assessing the severity of anxiety and depressive symptoms during the past week. The instrument is used for various indications associated with these symptoms. The instrument consists of 14 questions, which are grouped into 2 subscales, anxiety symptoms and depressive symptoms, each with 7 items. The questions on the 2 subscales alternate in the questionnaire. All questions are answered on Likert scales from 0 to 3, with 0 indicating a normal state and 3 indicating the highest level of anxiety or depression. The HADS subscales can each take values from 0 to 21 points. A score of 0 to 7 points is interpreted as normal, 8 to 10 points provide an indication of anxiety or depression, and values ≥ 11 show the probable presence of these disorders [13,14].
- The Numeric Rating Scale (NRS) is a patient-reported instrument with a one-dimensional Likert scale that assigns the most severe pain experienced in the last 24 hours to a number between 0 and 10. A higher number corresponds to more severe pain (no pain = 0, most severe pain imaginable = 10). Responders are defined as patients who had a score of at least 3 at baseline and whose pain reduction was at least 30% and at least 1 point on the scale [15,16]. As explained in the Institute's General Methods [17], in order for a response criterion to reliably reflect a change that is noticeable to patients, it should be predefined to correspond to at least 15% of the scale range of an instrument. For the analysis of the data in the study, for example, patients with a value of 3 at baseline were considered responders if the value was reduced to 2 after 16 weeks. However, this change corresponds to only about 9% of the scale range. Therefore, the analyses of the continuous data were used.

- The patient-reported Dermatology Life Quality Index (DLQI) consists of 10 items covering symptoms and feelings (2 items), daily activities (2 items), leisure time (2 items), work and school (1 item), personal relationships (2 items), and adverse effects of treatment (1 item). The items are answered using a 3-point or 4-point Likert scale or with yes or no. The answers relate to the past week. The total score ranges from 0 to 30, with lower scores corresponding to a higher health-related quality of life [18,19]. Responders were defined as patients whose total score decreased by at least 4 points [20]. However, this change corresponds to only about 13% of the scale range. Therefore, the analyses of the continuous data were used.

4.4 Assessment of the risk of bias in the results

The risk of bias was rated as low across all outcomes for the RELIEVE RCT (see Section A3.2.2 of the full report). The patients and treating physicians were not blinded. The other criteria — generation of the randomization sequence, allocation concealment, non-selective reporting, and other aspects across outcomes — were assessed as being fulfilled. Although data on the Severity Assessment of Hidradenitis Suppurativa (SAHS) were missing, which should have been collected according to the study protocol [10], the criterion "non-selective reporting" was nevertheless assessed as being fulfilled overall, as explained below: The SAHS forms a score (scale from 0 to 15) based on the number of affected skin regions, the number of inflammatory and/or painful lesions (excluding fistulas), number of fistulas, number of new or ruptured boils within the last 4 weeks, and pain assessment with an NRS. Disease severity is classified as mild (≤ 4 points), moderate (5 to 8 points), and severe (≥ 9 points) [21]. These symptoms of SAHS are also found in the IHS4 (see Section 4.3) and in the reported NRS, so that no data were withheld, but only a further operationalization of the severity of the disease in the form of SAHS was not reported. No reason was given for the missing SAHS data. One possible explanation could be the aforementioned redundancy in content compared to the other instruments, which would have further exacerbated the existing problem of multiplicity (see Section 4.3). Overall, it is not assumed that the reporting was selective.

The intention-to-treat (ITT) principle is one of the factors relevant for assessing the outcome-specific risk of bias. As already explained in Section 4.2, the intervention group was more severely affected by the pandemic measures than the control group. This was due in particular to the fact that the combined skin irradiation using IPL and RF was performed at the study centres. Patients in the control group, on the other hand, were able to apply the TAB independently and in full at home despite the COVID-19 pandemic. The ITT principle was adequately implemented due to the MMRM analyses. The risk of bias for the criteria of non-selective reporting and absence of other aspects was also rated as low for all patient-relevant outcomes. The only differences between the outcomes were in the blinding of the outcome assessment. The outcome of treatment response (disease severity) was assessed by a blinded physician. In principle, the perception of the severity of a skin disease can be substantially

influenced by the expectations of non-blinded patients in a study. However, due to the extreme histological severity of the therapeutic indication being evaluated, this influence was considered negligible, so that the outcome-specific risk of bias was rated as low (high qualitative certainty of results). In contrast, the outcomes of anxiety and depressive symptoms, pain, and health-related quality of life were assessed subjectively by the non-blinded patients, which is why the risk of bias in this regard was rated as high (moderate qualitative certainty of results). The risk of bias in the assessment of adverse effects was rated as high due to the non-blinded assessment by medical or nursing staff (moderate qualitative certainty of results).

4.5 Results for patient-relevant outcomes

For the present benefit assessment, the results after 16 weeks were used for all patient-relevant outcomes.

4.5.1 Results for the outcome of treatment response (disease severity)

For the outcome of treatment response (disease severity), the proportion of responders based on the blinded outcome assessment by a physician after 16 weeks was 61.5% in the intervention group and 33.3% in the control group. There was a statistically significant effect in favour of combined skin irradiation using IPL and RF plus TABs (odds ratio [OR]: 3.20; 95% confidence interval [CI]: [1.27; 8.09]; p = 0.015; IQWiG's own calculation). The HiSCR analyses do not contradict this (not shown). This provides an indication of a greater benefit of combined skin irradiation using IPL and RF plus TABs compared to TABs alone for the outcome of treatment response (disease severity).

4.5.2 Results for the outcome of anxiety symptoms and depressive symptoms

For the patient-reported outcome of anxiety and depressive symptoms, analysed as the mean change in scores after 16 weeks compared to baseline, there were no statistically significant differences between the 2 groups for the anxiety subscale (mean difference [MD]: 0.60; 95% CI: [−0.60; 1.80]; p = 0.457) and the depressive symptoms subscale (MD: −0.90; 95% CI: [−2.11; 0.31]; p = 0.107). There is therefore no hint of greater benefit or greater harm from combined skin irradiation using IPL and RF plus TABs compared to TABs alone for the outcomes of anxiety symptoms and depressive symptoms.

4.5.3 Results for the outcome of pain

For the patient-reported outcome of pain, analysed as the mean change in scores after 16 weeks compared to the baseline scores, the mean change for combined skin irradiation using IPL and RF plus TABs was −2.3 (standard deviation [SD]: 3.6) and for TABs alone was −0.9 (SD: 2.5). There was a statistically significant effect in favour of combined skin irradiation using IPL and RF plus TABs (MD: −1.40; 95% CI: [−2.78; −0.02]; p = 0.007). The standardized effect

(Hedges' g) was −0.45; however, the 95% CI for this effect [−0.89; 0.00] covered the irrelevance threshold of −0.2. Thus, there is a possibility that this effect lies in an irrelevant range. Therefore, for the outcome of pain, there is no hint of greater benefit or greater harm from combined skin irradiation using IPL and RF plus TABs compared to TABs alone.

4.5.4 Results for the outcome of surgical interventions

No results were reported for this outcome in the included study.

4.5.5 Results for the outcome of health-related quality of life

For the patient-reported outcome of health-related quality of life, analysed as the mean change in scores after 16 weeks compared to baseline, the mean change for combined skin irradiation using IPL and RF plus TABs was −4.6 (SD: 4.7) and for TABs alone was −1.6 (SD: 6.2). There was a statistically significant effect in favour of combined skin irradiation using IPL and RF plus TABs compared to TABs alone (MD: −3.00; 95% CI: [−5.43; −0.57]; p = 0.019). The standardized effect (Hedges' g) was −0.54; however, the 95% CI for this effect [−0.98; −0.10] covered the irrelevance threshold of −0.2. Thus, there is a possibility that this effect lies in an irrelevant range. Therefore, for the outcome of health-related quality of life, there is no hint of greater benefit or greater harm from combined skin irradiation using IPL and RF plus TABs compared to TABs alone.

4.5.6 Results on adverse effects

By Week 16, 307 combined IPL and RF skin irradiations had been performed. As a result of specific AEs being queried exclusively in the intervention group, 51 AEs were documented in 12 of the 43 patients (27.9%). The most common were redness (n = 18) and swelling (n = 14). According to the authors, all specific AEs were temporary. When further AEs were examined, 2 and 4 events were documented in the intervention and control groups, respectively (see Table 18 of the full report). The AEs were not collected systematically and equally in both groups. In addition, the results of the individual AEs were not analysed as "patients with events." However, the clear disadvantage of the intervention in terms of the ratio of AEs that occurred cannot be explained solely by the different data collection methods or the non-transparent presentation in the groups, but can also be attributed to the combined skin irradiation using IPL and RF.

No analyses of discontinuations due to AEs were available. According to the publication, 1 patient in the intervention group discontinued the study due to nausea and vomiting, but there is no systematic analysis covering all patients who had an AE that led to discontinuation of treatment.

No analyses of severe AEs and serious adverse events (SAEs) were reported. According to the study protocol[3] , this can be interpreted to mean that neither severe AEs nor SAEs occurred.

The analysis of Period B does not provide any additional insights regarding adverse effects.

With regard to adverse effects, there is a hint that combined skin irradiation using IPL and RF plus TABs causes greater damage than TABs alone.

4.6 Summary assessment of the results

Map of evidence

The following Table 3 shows the evidence map in relation to patient-relevant outcomes.

Table 3: Map of evidence in relation to patient-relevant outcomes

Morbidity				QoL	Adverse effects			
Treatment response (disease severity)	Anxiety symptoms and depressive symptoms	Pain	Surgical interventions	Health-related quality of life	AEs	Discontinuations due to AEs	Severe AEs	SAEs
⇑	⇔	⇔	–	⇔	↘	–	(⇔)	(⇔)

⇑: Indication of greater benefit of combined skin irradiation using IPL and RF plus TABs compared to TABs alone.
↘: Hint of greater harm from combined skin irradiation using IPL and RF plus TABs compared to TABs alone.
⇔: No hint, indication, or proof in favour of the intervention or control group.
(⇔): No hint, indication, or proof in favour of the intervention or control group; no events occurred.
–: no usable data reported

AE: adverse event; IPL: intense pulsed light; QoL: (health-related) quality of life; RF: radiofrequency; SAE: serious adverse event; TABs: topical antibiotics.

Assessment of the extent of unpublished data

No relevant studies without reported results were identified. Therefore, there was no limitation of the certainty of the conclusions in this benefit assessment.

[3] "Patients and test subjects will be clinically monitored before, during, and after treatment. No serious adverse effects of the treatment are to be expected. Should complications arise contrary to expectations, these will be documented and recorded..." (translated from German [10]).

Benefit-harm balance

A total of 1 RCT was included in the present benefit assessment. Based on this study, there was an indication of a greater benefit of combined skin irradiation using IPL and RF plus TABs compared to TABs alone for the outcome of treatment response (disease severity). For the outcomes of anxiety symptoms, depressive symptoms, pain, and health-related quality of life, there was no hint of greater benefit or greater harm of the test intervention compared to the control intervention. With regard to adverse effects, there was a hint of greater harm from combined skin irradiation using IPL and RF plus TABs compared to TABs alone for the outcome of AEs.

Overall, the outcome of treatment response (disease severity) was considered to be of high importance, as it reflects the treatment goal. In contrast, the AEs were considered to be of low importance, as they were only temporary and not severe (mostly redness and swelling). Therefore, across all outcomes, there was an indication of a greater benefit of combined skin irradiation using IPL and RF plus TABs compared to TABs alone.

5 Classification of the assessment result

5.1 Patients with severe HS/AI

In accordance with the G-BA mandate, patients with Hurley Stage I or II HS/AI were the target population for this assessment (see Chapter 2). The Hurley score is a widely used tool for classifying the severity of the disease. Other tools are also available (see Chapter 1). The search strategies were very sensitive with regard to the population, so that the severity of the disease and the tool used were not included in the search syntax (see Section A.1). Therefore, during the screening and selection process, ongoing and completed RCTs with the test and control interventions according to the research question would also have been identified that included or separately analysed patients with Stage III HS/AI or that used a different instrument to classify the severity of the disease, such as the IHS4. However, neither of these was the case. Therefore, no high-quality evidence on the use of combined skin irradiation using IPL and RF plus TABs for patients with severe HS/AI is to be expected at present or in the foreseeable future.

5.2 Combined skin irradiation using IPL and RF as maintenance therapy

Combined skin irradiation using IPL and RF as maintenance therapy was not the subject of this benefit assessment. As explained below, Period B of the RELIEVE RCT is not suitable for answering this question: In the RELIEVE RCT, all patients received combined skin irradiation using IPL and RF after completion of Period A, regardless of the original randomization. Period B could be interpreted as maintenance therapy for patients who received combined skin irradiation using IPL and RF plus TABs in Period A. However, since all patients in Period B received combined skin irradiation using IPL and RF as monotherapy, there is a lack of suitable comparative data for calculating the effect, among other things. Therefore, the study design in particular is not suitable for evaluating combined skin irradiation using IPL and RF as maintenance therapy.

5.3 Special aspects relating to patient-relevant outcomes

The RELIEVE RCT was conducted during the COVID-19 pandemic, which had a major impact on the study. The impact of the lockdowns has already been described in Section 4.2. Among other things, 10 patients were treated with fewer combined skin irradiations with IPL and RF than planned, so that an underestimation of the effect of the test intervention can be assumed for the outcomes of treatment response (disease severity), pain, health-related quality of life, and for specific AEs. The outcome of anxiety and depressive symptoms is a special case: the authors of the RELIEVE RCT publication consider it possible that the results for this outcome may have been distorted by the COVID-19 pandemic, as this situation placed an extraordinary burden on all patients. This assumption is understandable, meaning that a possible effect of the test intervention may have been masked.

In the RELIEVE RCT, no results were available for the outcome of surgical interventions, which is plausible given the short duration of the study. According to the study protocol, no further examinations were planned after Week 32. Following discussions with affected patients, this outcome was added as relevant for the assessment, as affected patients are counting on combined skin irradiation using IPL and RF to reduce or even avoid surgical interventions. Early use was therefore described as a gentle, potential alternative to surgical intervention. One patient reported a recent major reconstructive surgery that was very traumatic and that she regretted in retrospect. The surgical intervention was compared to an amputation, and the recovery process took about 6 months, during which she felt "torn from life."

No analyses of severe AEs and SAEs were available in the present assessment. As already explained in Section 4.5.6, it can be assumed that no events occurred. According to further literature, no severe AEs and SAEs are known [2,22-24].

5.4 Relevant aspects for patients that were not covered by this benefit assessment

In order to in particular discuss patient-relevant outcomes for this benefit assessment, an exchange with 5 affected patients, who were all familiar with combined IPL and RF skin irradiation, took place at the beginning of the project. During this discussion, in addition to the clear focus on alleviating symptoms and pain — and thus improving quality of life — other aspects were raised by these patients that were not covered by this benefit assessment. As these were of great importance to them and represent possible starting points for improving the overall situation of patients with HS/AI, they are addressed below.

According to the affected patients, who have been suffering from the disease for several years and are familiar with all stages, the combined skin irradiation using IPL and RF has a positive effect on the course of the disease in all degrees of severity, including Stage III. Therefore, there was a desire not to limit the therapeutic indication to individual degrees of severity. In addition, they pointed out that symptomatic therapy lasting only a few weeks is insufficient in view of the lifelong nature of the disease. Based on their experience, they appealed for the combined skin irradiation of IPL and RF to be used not on a short-term basis, but continuously as a maintenance therapy (even without parallel antibiotics). Furthermore, based on their experiences, patients considered it sensible for the application of combined skin irradiation using IPL and RF to be determined individually by the physician, as a non-individually determined number of sessions per year (quotas) or a rigid treatment rhythm was considered insufficiently flexible. Furthermore, the experiences with wound centres were highlighted as positive, as they specialize in wound treatment, unlike most medical practices.

Patient care does not refer exclusively to treatment, but also includes diagnosis. In discussions with affected patients, it was reported several times that it took several years to reach a diagnosis. In one case, it was not the treating physicians but someone from an obesity group

who pointed out the disease HS/AI. Furthermore, patients found questions about personal hygiene, weight, and smoking habits during examinations and treatments to be discriminatory ("an affront"). Medical advice (e.g., eat more sage, pay more attention to personal hygiene) was also described as "insolent" in some cases and therefore caused "anger" among affected patients, as they felt misunderstood and stigmatized. In addition, abscesses and fistulas are not immediately apparent to other people, so there is usually a lack of understanding of the condition (unlike "a broken arm"). In this context, the name acne inversa was criticized because the symptoms are significantly more severe than, for example, in acne vulgaris. Due to the linguistic "similarity", many people who hear the term acne inversa for the first time mistakenly classify the disease as "harmless". Overall, affected patients would like to see more understanding for their condition in society and better medical and psychological care in the future.

Finally, the following quote from the discussion with affected patients provides an insight into the situation of people with the disease: HS/AI is "a disease that you can survive, but it is almost impossible to live with."

6 Conclusion

Data from a high-quality study provide an indication that, for patients with Stage I or II HS/AI, skin irradiation using a combination of IPL and RF plus TABs is more beneficial than TABs alone across all outcomes. This conclusion is particularly supported by the results for treatment response (disease severity), which showed substantially greater improvement in patients treated with the combination therapy. Any adverse events were temporary and not serious.

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The full list is included in the original report.

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The full report (German version) is published under
https://www.iqwig.de/en/projects/n24-01.html

Appendix A Search strategies

A.1 Searches in bibliographic databases

1. MEDLINE

Search interface: Ovid

- Ovid MEDLINE(R) ALL 1946 to May 22, 2024

The following filter was adopted:

- RCT: Lefebvre [25] – Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity-maximizing version (2023 revision)
- Systematic review: Wong [26] – High specificity strategy (adapted)

#	Searches
1	Hidradenitis Suppurativa/
2	(hidradenitis adj1 suppurativ*).ti,ab.
3	or/1-2
4	Intense Pulsed Light Therapy/
5	exp Radiofrequency Therapy/
6	exp Combined Modality Therapy/
7	exp Ambulatory Care/
8	(light* adj3 (therap* or intens* or pulse*)).ti,ab.
9	radiofrequency*.ti,ab.
10	laight*.ti,ab.
11	((multimodal* or (combined adj3 modalit*) or ambulator* or innovative* or non-invasive* or noninvasive*) adj3 (therap* or treatment* or care*)).ti,ab.
12	or/4-11
13	exp Randomized controlled Trial/
14	controlled clinical trial.pt.
15	(randomized or placebo or randomly or trial or groups).ab.
16	drug therapy.fs.
17	or/13-16
18	17 not (exp animals/ not humans.sh.)
19	Cochrane database of systematic reviews.jn.
20	(search or MEDLINE or systematic review).tw.
21	(meta analysis or systematic review).pt.
22	or/19-21
23	22 not (exp animals/ not humans.sh.)
24	and/3,12,18
25	and/3,12,23

#	Searches
26	or/24-25
27	26 and (english or german or multilingual or undetermined).lg.

2. Embase

Search interface: Ovid

- Embase 1974 to 2014 2024 May 22

The following filter was adopted:

- RCT: Wong [26] – Strategy minimizing difference between sensitivity and specificity

#	Searches
1	suppurative hidradenitis/
2	(hidradenitis adj1 suppurativ*).ti,ab.
3	or/1-2
4	intense pulsed light therapy/
5	exp radiofrequency therapy/
6	exp ambulatory care/
7	(light* adj3 (therap* or intens* or pulse*)).ti,ab.
8	radiofrequency*.ti,ab.
9	laight*.ti,ab.
10	((multimodal* or (combined adj3 modalit*) or ambulator* or innovative* or non-invasive* or noninvasive*) adj3 (therap* or treatment* or care*)).ti,ab.
11	or/4-10
12	(random* or double-blind*).tw.
13	placebo*.mp.
14	or/12-13
15	and/3,11,14
16	15 not medline.cr.
17	16 not (exp animal/ not exp human/)
18	17 not (Conference Abstract or Conference Review or Editorial).pt.
19	18 not ((afrikaans or albanian or arabic or armenian or azerbaijani or basque or belorussian or bosnian or bulgarian or catalan or chinese or croatian or czech or danish or dutch or english or esperanto or estonian or finnish or french or gallegan or georgian or german or greek or hebrew or hindi or hungarian or icelandic or indonesian or irish gaelic or italian or japanese or korean or latvian or lithuanian or macedonian or malay or norwegian or persian or polish or polyglot or portuguese or pushto or romanian or russian or scottish gaelic or serbian or slovak or slovene or spanish or swedish or thai or turkish or ukrainian or urdu or uzbek or vietnamese) not (english or german)).lg.

3. The Cochrane Library

Search interface: Wiley

- Cochrane Central Register of Controlled Trials: Issue 4 of 12, April 2024, Cochrane Database of Systematic Reviews: Issue 5 of 12, May 2024

#	Searches
1	[mh ^"Hidradenitis Suppurativa"]
2	(hidradenitis:ti,ab NEAR/1 suppurativ*:ti,ab)
3	#1 OR #2
4	[mh ^"Intense Pulsed Light Therapy"]
5	[mh "Radiofrequency Therapy"]
6	[mh "Combined Modality Therapy"]
7	[mh "Ambulatory Care"]
8	(light*:ti,ab NEAR/3 (therap*:ti,ab OR intens*:ti,ab OR pulse*:ti,ab))
9	radiofrequency*:ti,ab
10	laight*:ti,ab
11	(multimodal*:ti,ab OR (combined:ti,ab NEAR/3 modalit*:ti,ab) OR ambulator*:ti,ab OR innovative*:ti,ab OR non-invasive*:ti,ab OR noninvasive*:ti,ab) NEAR/3 (therap*:ti,ab OR treatment*:ti,ab OR care*:ti,ab)
12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	#3 AND #12
14	#13 not (*clinicaltrial*gov* or *trialsearch*who* or *clinicaltrialsregister*eu* or *anzctr*org*au* or *trialregister*nl* or *irct*ir* or *isrctn* or *controlled*trials*com* or *drks*de*):so
15	#14 not ((language next (afr or ara or aze or bos or bul or car or cat or chi or cze or dan or dut or es or est or fin or fre or gre or heb or hrv or hun or ice or ira or ita or jpn or ko or kor or lit or nor or peo or per or pol or por or pt or rom or rum or rus or slo or slv or spa or srp or swe or tha or tur or ukr or urd or uzb)) not (language near/2 (en or eng or english or ger or german or mul or unknown))) in Trials
16	#3 in Cochrane Reviews

4. International HTA Database

Search interface: INAHTA

#	Searches
1	"Hidradenitis Suppurativa"[mh]
2	(hidradenitis AND suppurativ*)[Title] OR (hidradenitis AND suppurativ*)[abs]
3	#2 OR #1

A.2 Searches in study registries

1. ClinicalTrials.gov

Provider: U.S. National Institutes of Health

- URL: http://www.clinicaltrials.gov
- Type of search: Basic Search

Search strategy
(hidradenitis suppurativa) [Condition/disease] AND (laight OR pulsed light OR radiofrequency OR non-invasive OR noninvasive OR multimodal) [Other terms]

2. International Clinical Trials Registry Platform Search Portal

Provider: World Health Organization

- URL: https://trialsearch.who.int
- Type of search: Standard Search

Search strategy
(hidradenitis suppurativa OR acne inversa) AND (laight OR pulsed light OR radiofrequency OR non-invasive OR noninvasive OR multimodal)