Identification of unmet care needs, treatment preferences and health economic implications to optimize disease management outcomes in the field of chronic inflammatory skin diseases

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Table of Contents

1

General Introduction

This introductory chapter provides the background of the scientific research presented in this dissertation, entitled “Identification of unmet care needs, treatment preferences and health economic implications to optimize disease management outcomes in the field of chronic inflammatory skin diseases”. Following an initial description of the therapeutic areas, key concepts of this dissertation are explained, including unmet care needs, patient preferences & discrete-choice experiments, health economics & health technology assessments, cost-effectiveness analyses and systematic literature reviews. This chapter ends with an explanation of the outline and rationale of this dissertation.

1.1. Chronic inflammatory skin diseases

Chronic inflammatory skin diseases are the fourth most common cause of all human disease with an estimated 20–25% of the population being affected(1,2). Patients with chronic inflammatory skin diseases experience symptoms including itching, dry skin and changes in skin appearance to varying degrees of severity and bodily involvement with most patients suffering from high levels of psychological and quality of life impairment(1). It is not only the individual patient who carries the burden of their disease, but this burden often extends to their partners, caregivers and society(2). Atopic dermatitis (AtD), psoriasis (PSO), and hidradenitis suppurativa (HS) are among the most frequent chronic inflammatory skin diseases with prevalence rates in adults of 2-10%(3-5), 2-3%(6-8) and 0.1-1.3%(9-11), respectively. The annual patient costs of these diseases are consistently reported between €4,000 and €10,000 in Europe and these costs may increase even further if patients are not well managed or experience severe forms of these diseases(12-14). Whilst significant improvements in diagnosis and management have been observed in recent years, several challenges remain. Systemic immunosuppression is the treatment goal for almost all of these diseases, but often does not lead to remission or cure(1). Adverse events due to systemic immunosuppression, insufficient therapeutic effectiveness to achieve desired treatment outcomes or relapses of disease frequently occur. These factors cause low treatment adherence and satisfaction rates which highlight the need to understand the unmet care needs and account for patients’ preferences in healthcare decision-making in order to improve management outcomes(15).

1.2. Unmet care needs

The concept of unmet care needs is broad and usually encompasses either the burden of (non-)available treatments, patient population size, or disease severity. From a patient perspective, unmet care needs are circumstances where

no satisfactory method of diagnosis, prevention or treatment exists or is not accessible. In other words, unmet care needs either arise from patients being unable or unwilling to receive satisfactory diagnosis, prevention or treatment for their health problems(16).

1.3. Patient preferences & discrete-choice experiments

Patients have growing knowledge of their health and disease which offers unique opportunities to gain insights into their condition, unmet care needs and treatment experiences. The patient perspective, which can differ from those of physicians, drug manufacturers, health policy-makers and regulators, is often missing when healthcare decisions are made on behalf of the patients(17). In the future, a greater focus on patient preferences in clinical practice guidelines, academic research, drug development, regulatory- and reimbursement decision-making is expected to align health interventions' attributes, benefits and costs with patient preferences which in turn can improve uptake, adherence, and patient satisfaction(18-22). Patient preference studies as scientific method offer the generation of data on patients' perceptions and preferences surrounding different aspects of health-related products, services, and interventions. Patient preference studies can be categorized into revealed-preference studies and stated-preference studies. Revealed preferences are assessed through real-life choices on a particular intervention or service while stated preferences are elicited on hypothetical choices. Despite stated-preference methods relying on hypothetical scenarios, they offer the advantage of measuring preferences in a controlled experimental setting, can more easily control the decision-making scenario and also allow to explore interventions or services that not yet exist(17). One of the most commonly used stated-preference method is the discrete choice-experiment (DCE). A DCEs is a survey-based method used to elicit preferences for health and health care by repeatedly asking respondents to choose between two or more alternatives, where at least one treatment attribute is systematically varied(23). By controlling the attribute levels experimentally and asking respondents to repeatedly make choices, a DCE allows to quantify the impact of changes in attribute levels on decision behaviour(24). In other words, it allows to understand which attribute among a range of attributes had the greatest influence on the decision-making of the patient towards a particular health intervention or service. Patient preference studies are a critical component to inform healthcare decision-making in e.g., Health Technology Assessments to meet the needs of patients.

1.4. Health economics & Health Technology Assessments

While economics is the theory of efficient allocation of resources for production, distribution, and consumption of goods and services, health economics is the dedicated field of economics focused on efficiency in the production and consumption of healthcare goods and services(25). Health Technology Assessments (HTA) is a multidisciplinary process in the field of health economic that uses explicit methods to determine the value of a health technology with the purpose to inform decision-making in order to promote an equitable, efficient, and high-quality health system(26). HTA has become an established policy tool in health economics to inform the resources allocated to existing and new pharmaceuticals, medical devices, and other technologies by carefully assessing their costs and benefits(25,27,28). To increase the success rate of future interventions in development, early-stage HTAs can additionally be conducted to predict the viability of new technologies and to inform the generation of appropriate evidence to maximize the likelihood of future acceptance and resource allocation(29,30). An HTA usually includes an economic evaluation like a cost-effectiveness analysis to compare the costs and effects of alternative health interventions.

1.5. Cost-effectiveness analyses

The primary objective of economic evaluations like cost-effectiveness analyses (CEA) is to provide valid and reliable information to healthcare policy-makers on the relative value of alternative healthcare interventions. In comparison to Cost-Benefit Analyses or Cost-Minimization Analyses which are simpler forms of economic evaluations, CEA is a more sophisticated method that evaluates the incremental outcomes and costs of interventions(31). The results are usually summarized as incremental cost-effectiveness ratio (ICER) which represents the changes in health benefits due to a new intervention, compared with a specific alternative, against the changes in costs. In many cases, the health benefits are calculated in quality-adjusted life years (QALYs) comparing a new intervention (therapy, diagnostic or prevention option). The incremental costs can include costs ranging from direct medical to non-medical indirect costs, depending on the preferred analysis perspective. Sensitivity analyses varying selected data, methods or assumptions are recommended in CEAs to test the robustness of the results(31). In many legislations, CEAs are required for reimbursement decisions as part of HTAs by demonstrating that the additional costs of a new technology are justified by the additional health benefits it offers against specific willingness-to-pay thresholds(25,32).

1.6. Systematic literature reviews

The increase in published healthcare research on unmet care needs, patient preferences, HTAs and cost-effectiveness analyses has led to a more frequent use of systematic literature reviews (SLRs). SLRs comprehensively identify, evaluate, and summarize the evidence of all individual studies on a specific topic. SLRs are highest ranked in the level of hierarchy in evidence-based medicine and are considered gold-standard evidence by HTA authorities in reimbursement decision-making (33-35). The key steps to conduct a robust SLR consist of framing the question, identifying relevant studies, assessing their quality, summarizing the evidence and interpreting the findings(36). For each of these steps in SLRs, specific guidelines are published to attain desirable quality and robustness. Within HTAs, SLRs are recommended to reliably identify all available evidence on e.g., clinical trials, HTAs, or cost-effectiveness analyses(35).

1.7. Rationale & outline of the dissertation

This dissertation identified the unmet care needs and preferences of patients with chronic inflammatory skin diseases and explored health economic implications of treatments to allow the optimization of disease management. These research efforts aimed to increase the understanding of the current constraints in the management of inflammatory skin diseases and were intended to reveal the treatment decision-making behavior from the perspective of patients to improve the disease management outcomes for patients. This dissertation is centered around six complementary research chapters (chapters 2 to 7), which are visualized in Figure 1-1. The chapters are presented in chronological order of development and publication, except for chapter 7 which was intentionally positioned last due to its focus on a distinct disease area.

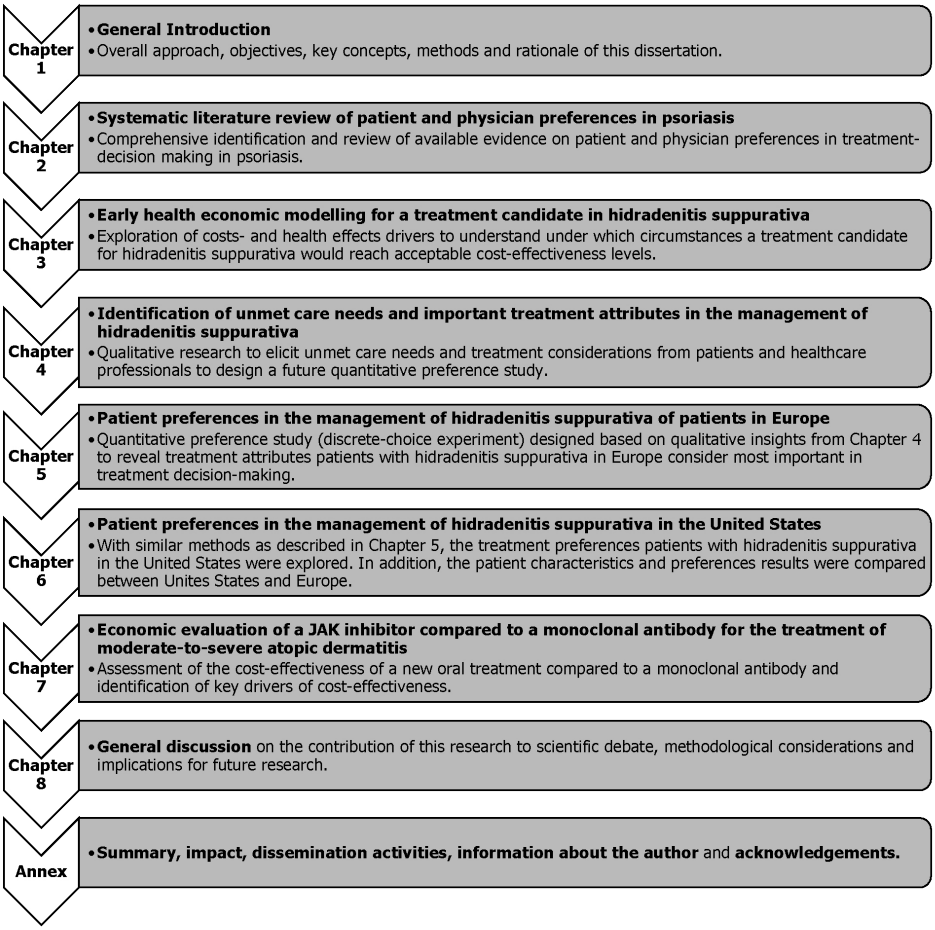


Figure 1 - 1: Visualization of the dissertation contents.
Note: JAK: Janus Kinase inhibitor.

To contribute towards reducing the high burden chronic inflammatory skin diseases place on patients and society, multiple patient-focused and health economics studies were conducted and published for this dissertation.

As initial research, an SLR was conducted to systematically identify, appraise the quality and summarize the wide array of available DCE studies reporting on treatment preferences of patients and physicians in PSO **(chapter 2)**. The synthesis of evidence of this SLR aimed provide a clearer evidence basis for future clinical-, drug development-, regulatory or reimbursement decision-making(37).

For the research highlighted in **chapter 3**, a 'de novo' early cost-effectiveness model was developed to assess the cost-effectiveness of a treatment candidate in HS. A targeted literature review of published clinical and economic studies and previous HTAs aided the development of a robust and reliable 'de novo' economic model that allowed to conclude under which circumstances in terms of costs, effectiveness and evaluation settings, a future treatment candidate for HS would reach acceptable cost-effectiveness levels for reimbursement. This research can support value demonstration of future treatments by having highlighted the drivers of cost-effectiveness and economic evidence requirements for reimbursement in HS(38).

Chapter 4 subsequently aimed to generate unprecedented insights into the unmet care needs and relevant treatment considerations from the perspective of patients and healthcare professionals (HCPs) in HS using qualitative methods across multiple European and North-American countries. Individual semi-structured interviews were conducted with HS patients (n=12) and HCPs (n=16) experienced in treating HS(39).

With the treatment attributes identified using qualitative interviews with patients and HCPs in chapter 4, the first quantitative preference study (DCE) with patients with HS in Europe was designed to reveal which treatment attributes patients considered most important in treatment decision-making **(chapter 5).** The finding of this DCE can support future joint patient-physician decision-making in the management of HS and also allow development-, regulatory-and reimbursement decision-making of future HS treatments according to the preferences of patients(40).

Due to known differences in care pathways for HS across geographies and due to the heterogenous nature of HS, a similar DCE as in Europe was conducted with HS patients in the United States in **chapter 6**. In addition, a formal comparison of the patient characteristics and preferences between respondents in the United States and Europe was provided to increase the validity and generalizability of the findings(41).

Similar to the research presented in chapter 3, a 'de novo' cost-effectiveness model was developed to assess the cost-effectiveness of a novel JAK inhibitor compared to a monoclonal antibody for the treatment of moderate-to-severe AtD in the United Kingdom and to identify key drivers of cost-effectiveness. By having formulated opportunities for future clinical-, cost- and quality of life evidence generation, this research in **chapter 7**, can support future reimbursement activities of investigational products in AtD aiming to reduce the high burden of disease(42).

Lastly, additional sections in this dissertation provide further background information on the research including a general summary, impact, research dissemination activities, information about the author and acknowledgements.

References (General Introduction)

1. Ujiie H, Rosmarin D, Schon MP et al. Unmet Medical Needs in Chronic, Non-communicable Inflammatory Skin Diseases. Front Med (Lausanne) 2022;9:875492.
2. Flohr C, Hay R. Putting the burden of skin diseases on the global map. Br J Dermatol 2021;184:189-190.
3. Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab 2015;66 Suppl 1:8-16.
4. Bylund S, Kobyletzki LB, Svalstedt M, Svensson A. Prevalence and Incidence of Atopic Dermatitis: A Systematic Review. Acta Derm Venereol 2020;100:adv00160.
5. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. PLoS One 2012;7:e39803.
6. Armstrong AW, Mehta MD, Schupp CW, Gondo GC, Bell SJ, Griffiths CEM. Psoriasis Prevalence in Adults in the United States. JAMA Dermatol 2021;157:940-946.
7. Iskandar IYK, Parisi R, Griffiths CEM, Ashcroft DM, Global Psoriasis A. Systematic review examining changes over time and variation in the incidence and prevalence of psoriasis by age and gender. Br J Dermatol 2021;184:243-258.
8. Damiani G, Bragazzi NL, Karimkhani Aksut C et al. The Global, Regional, and National Burden of Psoriasis: Results and Insights From the Global Burden of Disease 2019 Study. Front Med (Lausanne) 2021;8:743180.
9. Schneider-Burrus S, Lux G, van der Linde K et al. Hidradenitis suppurativa - prevalence analyses of German statutory health insurance data. J Eur Acad Dermatol Venereol 2021;35:e32-e35.
10. Sachdeva M, Shah M, Alavi A. Race-Specific Prevalence of Hidradenitis Suppurativa. J Cutan Med Surg 2021;25:177-187.
11. Liang YT, Yeh CJ, Huang JY, Wei JC. Epidemiology of hidradenitis suppurativa in Taiwan: A 14-year nationwide population-based study. J Dermatol 2021;48:613-619.
12. Augustin M, Misery L, von Kobyletzki L, Armario-Hita JC, Mealing S, Redding M. Unveiling the true costs and societal impacts of moderate-to-severe atopic dermatitis in Europe. J Eur Acad Dermatol Venereol 2022;36 Suppl 7:3-16.
13. Balogh O, Brodszky V, Gulacsi L et al. Cost-of-illness in patients with moderate to severe psoriasis: a cross-sectional survey in Hungarian dermatological centres. Eur J Health Econ 2014;15 Suppl 1:S101-9.
14. Gaspar K, Hunor Gergely L, Jenei B et al. Resource utilization, work productivity and costs in patients with hidradenitis suppurativa: a cost-of-illness study. Expert Rev Pharmacoecon Outcomes Res 2021:1-10.
15. Belinchon I, Rivera R, Blanch C, Comellas M, Lizan L. Adherence, satisfaction and preferences for treatment in patients with psoriasis in the European Union: a systematic review of the literature. Patient Prefer Adherence 2016;10:2357-2367.
16. Vreman RA, Heikkinen I, Schuurman A et al. Unmet Medical Need: An Introduction to Definitions and Stakeholder Perceptions. Value Health 2019;22:1275-1282.
17. Jackson Y, Janssen E, Fischer R et al. The evolving role of patient preference studies in health-care decision-making, from clinical drug development to clinical care management. Expert Rev Pharmacoecon Outcomes Res 2019;19:383-396.

18. Whitty JA, Fraenkel L, Saigal CS, Groothuis-Oudshoorn CGM, Regier DA, Marshall DA. Assessment of Individual Patient Preferences to Inform Clinical Practice. Patient 2017;10:519-521.
19. Forsythe LP, Szydlowski V, Murad MH et al. A systematic review of approaches for engaging patients for research on rare diseases. J Gen Intern Med 2014;29 Suppl 3:S788-800.
20. Johnson FR, Beusterien K, Ozdemir S, Wilson L. Giving Patients a Meaningful Voice in United States Regulatory Decision Making: The Role for Health Preference Research. Patient 2017;10:523-526.
21. Bouvy JC, Cowie L, Lovett R, Morrison D, Livingstone H, Crabb N. Use of Patient Preference Studies in HTA Decision Making: A NICE Perspective. Patient 2020;13:145-149.
22. Ostermann J, Brown DS, de Bekker-Grob EW, Muhlbacher AC, Reed SD. Preferences for Health Interventions: Improving Uptake, Adherence, and Efficiency. Patient 2017;10:511-514.
23. Wang H, Rowen DL, Brazier JE, Jiang L. Discrete Choice Experiments in Health State Valuation: A Systematic Review of Progress and New Trends. Appl Health Econ Health Policy 2023:1-14.
24. Hauber AB, Gonzalez JM, Groothuis-Oudshoorn CG et al. Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force. Value Health 2016;19:300-15.
25. Drummond MF, Schwartz JS, Jonsson B et al. Key principles for the improved conduct of health technology assessments for resource allocation decisions. Int J Technol Assess Health Care 2008;24:244-58; discussion 362-8.
26. O'Rourke B, Oortwijn W, Schuller T, International Joint Task G. The new definition of health technology assessment: A milestone in international collaboration. Int J Technol Assess Health Care 2020;36:187-190.
27. Kristensen FB, Husereau D, Huic M et al. Identifying the Need for Good Practices in Health Technology Assessment: Summary of the ISPOR HTA Council Working Group Report on Good Practices in HTA. Value Health 2019;22:13-20.
28. Huls SPI, Whichello CL, van Exel J, Uyl-de Groot CA, de Bekker-Grob EW. What Is Next for Patient Preferences in Health Technology Assessment? A Systematic Review of the Challenges. Value Health 2019;22:1318-1328.
29. Pham B, Tu HA, Han D et al. Early economic evaluation of emerging health technologies: protocol of a systematic review. Syst Rev 2014;3:81.
30. MJ IJ, Koffijberg H, Fenwick E, Krahn M. Emerging Use of Early Health Technology Assessment in Medical Product Development: A Scoping Review of the Literature. Pharmacoeconomics 2017;35:727-740.
31. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276:1172-7.
32. Eichler HG, Kong SX, Gerth WC, Mavros P, Jonsson B. Use of cost-effectiveness analysis in health-care resource allocation decision-making: how are cost-effectiveness thresholds expected to emerge? Value Health 2004;7:518-28.
33. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. Plast Reconstr Surg 2011;128:305-310.

34. Anderson R. Systematic reviews of economic evaluations: utility or futility? Health Econ 2010;19:350-64.
35. Mandrik OL, Severens JLH, Bardach A et al. Critical Appraisal of Systematic Reviews With Costs and Cost-Effectiveness Outcomes: An ISPOR Good Practices Task Force Report. Value Health 2021;24:463-472.
36. Khan KS, Kunz R, Kleijnen J, Antes G. Five steps to conducting a systematic review. J R Soc Med 2003;96:118-21.
37. Sain N, Willems D, Charokopou M, Hiligsmann M. The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments. Curr Med Res Opin 2020;36:1257-1275.
38. Willems D, Charokopou M, Evers S, Hiligsmann M. Early health economic modelling for a treatment candidate in hidradenitis suppurativa. J Med Econ 2020;23:1516-1524.
39. Willems D, Hiligsmann M, van der Zee HH, Sayed CJ, Evers S. Identifying Unmet Care Needs and Important Treatment Attributes in the Management of Hidradenitis Suppurativa: A Qualitative Interview Study. Patient 2022;15:207-218.
40. Willems D, Hinzpeter EL, Van der Zee HH et al. Patient Preferences in the Management of Hidradenitis Suppurativa: Results of a Multinational Discrete Choice Experiment in Europe. Patient 2023.
41. Willems D, Sayed CJ, Van der Zee HH et al. A discrete-choice experiment to elicit the treatment preferences of patients with hidradenitis suppurativa in the United States. J Med Econ 2023:1-9.
42. Heinz KC, Willems D, Hiligsmann M. Economic evaluation of a JAK inhibitor compared to a monoclonal antibody for treatment of moderate-to-severe atopic dermatitis from a UK perspective. J Med Econ 2022;25:491-502.

2

The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments

Chapter 2 was informed by:
Sain, N., Willems, D., Charokopou, M., & Hiligsmann, M. (2020). The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments. *Current Medical Research and Opinion*, 36(8), 1257-1275.

2.1. Abstract

Introduction: Treatment adherence remains to be a major challenge in psoriasis. Patient preference studies, especially discrete-choice experiments are gaining popularity to gather insights into patient-reported treatment outcomes. This systematic literature review aimed to critically assess all discrete-choice experiments exploring patients' and physicians' preferences for psoriasis treatment characteristics.

Methods: PubMed and EMBASE databases were searched using keywords "psoriasis" and "preferences" to identify relevant literature. Discrete-choice experiments conducted in French or English from the year 2000 onwards, that focused on evaluating psoriasis treatment preferences in patients and/or physicians were included. The relative importance of treatment attributes was assessed, and studies were critically appraised using validated checklists.

Results: Out of 987 articles identified, 25 articles fulfilled the inclusion criteria. Overall, patients and physicians prioritize efficacy-specific outcomes. Patients are shown to place greater importance to process attributes when compared to physicians, especially route and location of administration. Physicians focus primarily of efficacy attributes, however when top two attributes are considered, safety outcomes become increasingly considered important. 60% of studies conducted subgroup analyses, of which many reported associations between specific patient characteristics and preferences. Factors such as age, disease severity, duration of condition significantly affected preferences for treatment attributes.

Conclusions: This review provides insight into the types of attributes that patients and physicians value most, and therefore can help improve shared decision-making. The findings of this study also encourage regulatory agencies to continue integrating patient preferences in their decision-making.

2.2. Introduction

Psoriasis is a chronic inflammatory disease that predominantly affects the skin and joints. Epidemiological data has reported that the prevalence of psoriasis varies from 0.9% in the United States to over 8% in Norway(1). Psoriasis not only significantly increases the risk of comorbidities, especially psoriatic arthritis, depression, obesity, diabetes and cardiovascular disease(2), but many affected patients report that the disease has a significant impact on their quality of life(3). Consequently, this has significant societal and economic implications due to elements such as increased rates of absenteeism in patients suffering from psoriasis(4). Although new therapies have revolutionized psoriasis treatment, patient treatment adherence continues to be a major challenge(5). Despite improved efficacy, persistently low adherence rates indicate that an unmet patient need exists regarding treatment availability. Whether this unmet care need motivates a drive to explore new treatment options with increased efficacy, or to evaluate the value of procedural treatment factors such as the ease of administration, attention should aim to understand patient perspectives. Studies have demonstrated that low levels of adherence are exacerbated by individual beliefs regarding psoriasis treatment and low levels of involvement from healthcare professionals(6). Therefore, shared decision-making, and increased patient-involvement are of utmost importance in the successful treatment of psoriasis. Insights into patients' preferences and increasing patient involvement in prescribing decisions can positively influence adherence rates and satisfaction(5,6). In turn, improved adherence rates can both save scarce healthcare resources and positively impact the economy by decreasing associated and indirect costs of treatment such as unnecessary hospitalizations and productivity losses(7). The need to incorporate patient preferences in prescription decision-making is nowadays widely acknowledged(8). Patient preference studies are broadening our understanding of the factors that influence treatment selection and adherence beyond traditional efficacy and safety outcome measures(9). Preference elicitation studies generally categorize treatment characteristics in process, outcome and cost factors. Process factors typically consist of attributes such as mode of administration, treatment frequency or location of administration while outcome factors focus on efficacy or treatment adverse event (AE) profiles(10). Patient preference studies are helping healthcare professionals and regulatory agencies broaden their understanding of patient values and thus promote placing the patient at the focal point of treatment decision-making(11). The incorporation of patient preferences in the value assessments of new treatments has been advocated by regulatory agencies such as the Food and Drug Administration (FDA) in the United States(12) and Health Technology Assessment bodies such as the National Institute

for Health and Care Excellence (NICE) in the United Kingdom(13). More importantly, the fact that these studies are being increasingly considered in the health technology assessments of treatments and in policy-context is giving patients a strong voice at the decision table(14).

Patient preference studies are generally divided into stated- or revealed-preferred methods. The former utilizes surveys and questionnaires to understand the motivations of patients when making trade-off decisions for hypothetical yet real-life-like treatment choices. The latter is based on observing choices made in real-world settings. Given that observation opportunities are limited in the context of psoriasis treatment decision-making, patient preference studies have adopted stated-preferred methods(10). Discrete-choice experiments (DCE), commonly categorized as a type of Conjoint Analysis (CA), are a type of stated-preference method that are frequently used to investigate patient preferences regarding psoriasis treatment characteristics(15). In DCEs, patients are asked to make trade-off decisions and elicit their preference between two or more hypothetical treatment options, each being characterized by a unique profile of treatment attributes. By doing so, researchers can identify the relative importance participants place on one attribute over another. According to the International Society for Pharmacoeconomics and Outcomes Research' (ISPOR) guide on conjoint analysis, CA and DCEs are especially useful for quantifying preferences in healthcare due to the constrained nature of a consumer's choice of goods(16). Additionally, DCE results have been described as more reliable than other types of preference elicitation methods due to their ability to mimic real-world decision-making situations(17). More importantly the improved quality and validity of DCE studies are receiving more attention from policy-makers(18,19).

Due to the prolific nature of preferences studies, there is a need to consistently update our understanding of patient and physician preferences for psoriasis treatment. Furthermore, there is value in investigating whether preferences for treatment attributes are in fact as heterogeneous as previously reported. Patient preferences have been shown to vary greatly amongst subgroups, i.e., region, age, disease severity, etc.(9). In a German patient preference DCE, Schaarschmidt et al. identified that patients value certain process attributes over outcomes attributes, suggesting that patients pay more attention to attributes that affect lifestyle factors(20). However, this contrasts with other studies that demonstrate that patients value efficacy and safety over process attributes(21,22). Though Florek et al.'s recent systematic review provided a strong general overview of patient values as they differentiate between subgroups, there was minimal focus on assessing

the quality of the studies included and a much broader focus on general patient preference studies using a wide variety of preference elicitation methods(9). The objective of the current study was to evaluate the treatment attributes that patients and physicians consider the most important when selecting a given treatment for psoriasis and to highlight key quality gaps to improve the validity and adoption of DCE studies in wider contexts. To do so, the current systematic review identified all relevant DCE studies and conducted a critical appraisal of the studies included to determine the current standard of quality in conducting these types of studies. Importantly, this review aimed to provide recommendations to strengthen the validity of future studies being conducted based on the limitations raised by the review. This paper then proceeded to strengthen the current understanding of preferred treatment characteristics and aimed to determine whether patients and physicians have diverging priorities when selecting treatment.

2.3. Methodology

2.3.1. Research type and design

The current systematic literature review builds on two recent systematic reviews of patient preference studies in psoriatic treatment by Florek et al. (9) and Gonzalez et al.(23). This review focuses only on DCEs that evaluate patient and physician preferences. The review applied the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement and incorporates recommendations by Fink(24) and Yu et al. (25) in the identification of all relevant articles and the critical appraisal of selected studies. The exact methodology of the proposed study followed the four-phase approach elaborated by Liberati (26) and is illustrated in Figure 2-1.

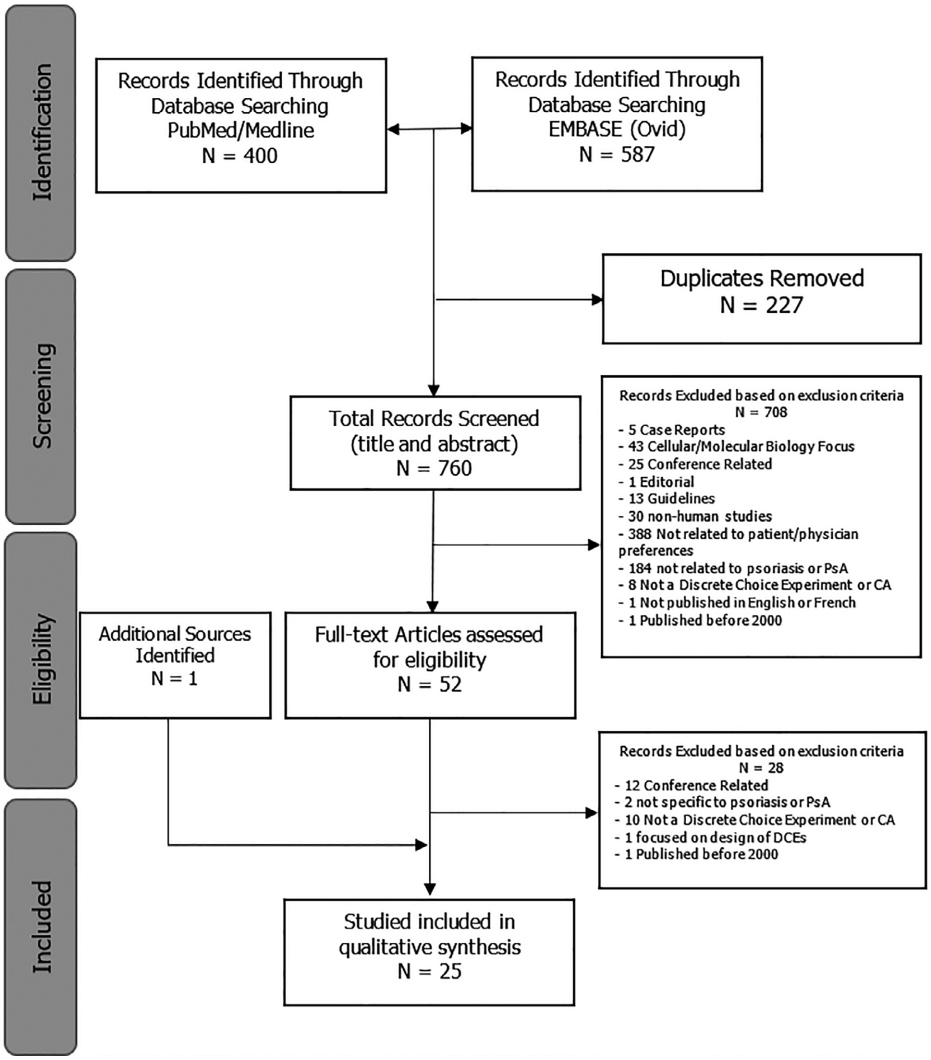


Figure 2 - 1: Selection and screening process referenced from Liberati et al.

2.3.2. Data collection

2.3.2.1. Identification/Search strategy

To identify all relevant literature, two databases were screened systematically: specifically, PubMed and EMBASE. The final search strategy utilized in this review derived key terms from three psoriasis-related studies and integrated the terms into a final comprehensive search strategy(9,27,28). The final search strategy combined two searches; the first being related to identifying preferences and the

second in relation to the therapeutic area of interest, psoriasis. The search strategy employed Boolean Operators in order to gather all relevant material; ((“preference*”) OR (“clinic* preference*”) OR (“physician* preference*”) OR (“patient* preference*”) OR (“patient* priorities”) OR (“public preference*”) OR (“discrete choice”) OR (“DCE”) OR (“conjoint analysis”) OR (“stated preference*”))) AND ((“Psoriasis”[MeSH Terms] OR “Psoriasis”[All Fields] OR “Psoria*” [Mesh Terms] OR “Psoria*” [All Fields]). This broad search strategy ensured that all studies regardless of naming convention were captured. To ensure comprehensiveness, the final selection was supplemented by a hand search. Both a backward and forward reference search strategy were employed on included studies and on related systematic literature reviews. Forward referencing identifies studies which have cited a study already included, whereas backward referencing refers to reviewing the bibliography of an article included in our review(29).

2.3.2.2. Screening and selection process

Key considerations were made in the screening process. Studies that related to both the treatment of psoriasis or psoriatic arthritis (PsA) were included given that there is significant overlap in the medications used to treat both in human beings(30). Secondly, studies had to include a discrete-choice exercise (a decision to be made between two or more options), be quantitative in nature and published (or in press) in a full-text English or French article between January 2000 and May 2019. This review excluded studies that did not use empirical measures to determine preferences such as surveys or focus groups. The current review also excluded any DCE that pooled psoriasis’ or PsA patients with other diagnoses (typically rheumatoid arthritis, ankylosing spondylitis) to avoid misinterpreting treatment selection preferences for other conditions. Lastly, case reports, commentaries, editorials, conference abstracts and unpublished articles as well as all grey literature were not included.

The systematic literature review employed a two-stage selection process according to PRISMA standards(26). The screening process was conducted by two independent researchers to ensure the internal validity of the process. During the first phase, the primary reviewer overviewed the titles and the abstracts of the papers identified in PubMed and EMBASE and screened them for relevance based on the inclusion and exclusion criteria specified above. The second reviewer validated the selection using the same criteria. In the second stage, selected articles underwent a full text screening by two independent researchers.

2.3.3. Data extraction and reporting quality assessment

Data extraction and quality reporting was carried out in a four-step process. Firstly, generic study characteristics were extracted. Extracted characteristics included title, author, year of publication, country, population, sample size, and DCE methodology characteristics (number of choice sets, number of attributes and number of alternatives). The second segment of the data analysis comprised of a quality assessment, integrating elements from two tested quality checklists. Firstly, it incorporated specific items from the ISPOR checklist which lays out best practices for conducting conjoint analysis(31). Specifically, this review included numerical items 2. Attributes and levels, 3. Construction of tasks, 4. Experimental design and 5. Preference elicitation from the checklist. These sections were drawn specifically to provide a more detailed assessment of the methodology of the studies included which are known to be typically lacking in quality(32). Secondly the PREFS (Purpose, Respondents, Explanation, Findings, Significance) checklist was used. All five elements of the PREFS checklist were used to assess quality namely; purpose (regarding the research question), respondents (regarding the internal and external validity), explanations (regarding the methodology, findings (regarding the results and conclusions) and significance (regarding the statistical analyses conducted)(33). Each item was scored based on whether it was acceptable (score = 1), needs improvement (score = 0.5) or was unacceptable (score = 0). An "acceptable" score represented a study that both reviewers answered 'yes' to the qualification questions to each section in both the PREFS and ISPOR checklist, "needs improvement" represented if at least one question was answered with a 'yes', whereas "unacceptable" was denoted by the reviewers answering 'no' to all qualifying questions. An aggregate sum score (ranging 0-9, whereas 9 equated to the maximal score) was then given to each study and was compared across studies. In the third step, all process, outcome and cost treatment attributes were identified for each study. Given variability in both the types and in the nomenclature of attributes, the attributes were categorized for ease of analysis purposes. Process attributes were divided into location (of administration), frequency (of administration), duration (of administration), delivery method and other; whereas outcome attributes were categorized as either efficacy specific, safety or quality of life specific. The efficacy and safety categories were further sub-categorized to simplify the interpretation of the various methods used for measuring safety and efficacy. Allocation of raw attributes into each specified category was confirmed by an independent reviewer with expertise in psoriasis. In the final step, the top two most important attributes for both patients and physicians from each study were identified. Each study's top two attributes were then tabulated and graphically represented. It is important to note that when reporting results, any process attribute that was

identified as being within the top two most important factors in a given study was labelled as a 'process attribute' instead of its specific sub-category to simplify the interpretation of the results. Also, PsA patients were agglomerated with PSO patients, given the limited number of studies and due to the similar nature of the treatments prescribed for both conditions. To structure the analysis of preferences for psoriasis treatment attributes, the number of times a given attribute category was identified as being most important in all studies was compared. Studies were categorized by either patient-specific or physician-specific and thus were compared only amongst themselves. Secondly, studies were also categorized by attributes design (outcome only vs. process and outcome vs. process, outcome and cost). The relative importance of each attribute within the studies was then reported. When the relative importance of an attribute was available in a study reviewed, the relative importance was drawn directly from the study. However, when only the coefficients were provided, the relative importance was calculated using the range level method discussed by ISPOR(34).

2.3.4. Exploratory analysis

In the final part of the review, we isolated studies that conducted subgroup analysis. Studies that included subgroup analysis were reviewed to identify qualifying characteristics that significantly impacted the preference associated with a given attribute. This review only highlighted specific associations between patient characteristics and attribute preferences if at least two studies demonstrated statistically significant results. Given that an analysis for every observable sub-group is beyond the scope of this review, this review builds on some of the characteristics reported by Florek et al. (9). Namely, we reported associations for age, marital status, disease severity, disease duration, impact of psoriasis on quality of life as measured by the Dermatology Life Quality Index (DLQI) and lastly comorbidity of PsA.

2.4. Results

Figure 2-1 illustrates the results of the study screening and selection process. By searching PubMed and EMBASE, 987 hits were obtained, 227 duplicate records were removed. Of the 760 records that remained, 708 records were excluded after title and abstract screening (Appendix). 52 articles underwent full-text assessment, of which only 24 articles met the full inclusion criteria. Only one additional article was identified through manual search, resulting in a total of 25 articles for the analysis.

2.4.1. Study characteristics

The main study characteristics are provided in Table 2-1 whereas categorical analyses of study characteristics are reported in the Appendix. Among the studies reviewed, the majority of published DCE studies were conducted since 2015 (64%)(17,21,22,35-45). Most studies were conducted in Europe (64%)(5,20,40,46-54) wherein 36% of all studies were conducted in Germany(5,20,22,35,42,49-51,53). Almost a quarter of all studies were conducted in the United States (24%)(17,21,38,43,48). Only 12% of all studies were conducted in Asia(39,41,45); one of which was conducted in a lower-middle income country (LMIC) (Philippines)(39). Sample sizes ranged from 67(39) to 1064(21). Finally, regarding the target population of the studies included, six studies included psoriasis patients with all degrees of severity whereby diagnosis was confirmed by a physician(21,37,38,45,47,48), eleven studies targeted solely patients with moderate-severe diagnosis(5,20,22,35,39,49-54), two studies targeted patients with concomitant psoriatic arthritis(36,43), two studies investigated physician preferences uniquely(44,46) while four studies investigated both patient and physician preferences(17,40-42).

Table 2 - 1: List of Discrete-Choice Experiment studies included in the systematic literature review of patient and physician preferences; including general characteristics of the studies.

Study	Author	Publication Year	Country	Subjects Included	Sample Size	DCE Design Characteristics	Industry funded
Trade-offs between the benefits and risks of drug treatment for psoriasis: a discrete choice experiment with U.K. dermatologists.	Ashcroft et al.	2006	United Kingdom	Practicing Dermatologists in the U.K. who are members of the British Association of Dermatologists (BAD)	227	2 sets of 8 choice sets 6 Attributes 2 Alternatives	No
Balancing the benefits and risks of drug treatment: a stated-preference, discrete choice experiment with patients with psoriasis.	Seston et al.,	2007	United Kingdom	Patients with Psoriasis	126	2 sets of 8 choice sets 6 Attributes 2 Alternatives	No
The value to patients of reducing lesion severity in plaque psoriasis.	Hauber et al.,	2011	United States	Patients with a self-reported diagnosis of plaque psoriasis from a nationally representative US household panel	419	9 choice sets 6 Attributes 2 Alternatives	Yes
Patient preferences for psoriasis treatments: process characteristics can outweigh outcome attributes.	Schaarschmidt et al.,	2011	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use	163	24 choice sets 11 Attributes 2 Alternatives	No
Comorbidities significantly impact patients' preferences for psoriasis treatments.	Schmieder et al.	2012	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use	163	24 choice sets 11 Attributes 2 Alternatives	No

Table 2 - 1: List of Discrete-Choice Experiment studies included in the systematic literature review of patient and physician preferences; including general characteristics of the studies.

Study	Author	Publication Year	Country	Subjects Included	Sample Size	DCE Design Characteristics	Industry funded
It is not always about gains: utilities and disutilities associated with treatment features in patients with moderate-to-severe psoriasis.	Umar et al..	2012	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use	163	24 choice sets 11 Attributes 2 Alternatives	No
Patient preferences for psoriasis treatments: impact of treatment experience.	Schaarschmidt et al., 2013	2013	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use	163	24 choice sets 11 Attributes 2 Alternatives	No
Matching physicians' treatment recommendations to patients' treatment preferences is associated with improvement in treatment satisfaction.	Umar et al., 2013	2013	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use	132	24 choice sets 11 Attributes 2 Alternatives	No
Eliciting preferences to inform patient-centered policies: the case of psoriasis.	Torbica et al., 2014	2014	Italy	Patients with moderate to severe plaque-type psoriasis	244	27 choice sets 5 Attributes 2 Alternatives	Yes
Psoriasis patients' willingness to accept side-effect risks for improved treatment efficacy.	Kauf et al., 2015	2015	United States	Patients with a self-reported physician diagnosis of plaque psoriasis	1608	48 choice sets 6 Attributes 2 Alternatives	Yes
Patient Preferences for Treatment of Psoriasis with Biologicals: A Discrete Choice Experiment.	Kromer et al., 2015	2015	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use	200	24 choice sets 11 Attributes 2 Alternatives	No

Table 2 - 1: List of Discrete-Choice Experiment studies included in the systematic literature review of patient and physician preferences; including general characteristics of the studies.

Study	Author	Publication Year	Country	Subjects Included	Sample Size	DCE Design Characteristics	Industry funded
Patient Preferences for Biologicals in Psoriasis: Top Priority of Safety for Cardiovascular Patients.	Schaarschmidt et al., 2015	2015	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use	200	24 choice sets	No
A discrete choice experiment to explore patients' willingness to risk disease relapse from treatment withdrawal in psoriatic arthritis.	Rothery et al., 2016	2016	United Kingdom	PsA patients considered to have minimal disease activity on the Bradford Psoriatic Arthritis Disease Register	136	12 choice sets 3 Attributes 2 Alternatives	No
Dermatologist and Patient Preferences in Choosing Treatments for Moderate to Severe Psoriasis.	Alcusky et al., 2017	2017	United States	Physicians that both specialize in and are board-certified/eligible in dermatology - Patients has moderate to severe psoriasis based on self-report of symptoms	200 Physi-cians 196 patients	16 choice sets 7 Attributes 3 Alternatives	Yes
Evaluation of psoriasis patients' attitudes toward benefit-risk and therapeutic trade-offs in their choice of treatments.	Eliasson et al., 2017	2017	United Kingdom	Patients with formal psoriasis diagnosis and 3+ palm areas or 3% of body surface area (BSA) affected	292	32 choice sets 6 Attributes 2 Alternatives	Yes
What is clearance worth? Patients' stated risk tolerance for psoriasis treatments.	Fairchild et al., 2017	2017	United States	Patients with a physician confirmed diagnosis of psoriasis	927	40 choice sets 5 Attributes 2 Alternatives	Yes

Table 2 - 1: List of Discrete-Choice Experiment studies included in the systematic literature review of patient and physician preferences; including general characteristics of the studies.

Study	Author	Publication Year	Country	Subjects Included	Sample Size	DCE Design Characteristics	Industry funded
Patient preference on psoriasis treatment in a Philippine Tertiary Hospital: A conjoint analysis.	Guevara et al., 2017	2017	Philippines	Patients clinically diagnosed with moderate to severe psoriasis according to Psoriasis Area and Severity Index (PASI) score	62	18 choice sets 7 Attributes 2 Alternatives	No
Comparing preferences for outcomes of psoriasis treatments among patients and dermatologists in the U.K.: results from a discrete-choice experiment.	Gonzalez et al., 2017	2017	United Kingdom	Patients that had moderate to severe psoriasis corroborated using a DLQI questionnaire	174 patients 100 dermatologists	48 choice sets 5 Attributes 2 Alternatives	Yes
Treatment preferences for biologicals in psoriasis: experienced patients appreciate sustainability.	Kromer et al., 2017	2017	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use	200	24 choice sets 11 Attributes 2 Alternatives	No
Patient and Physician Preferences for Therapy Characteristics for Psoriasis: A Discrete Choice Experiment in Japan.	Bolt et al., 2018	2018	Japan	Patients with diagnosis at least a year and are actively receiving treatment + moderate or severe - Physicians having to treat moderate to severe psoriasis patients each month	306 patients 161 physicians	16 choice sets 7 Attributes 2 Alternatives	Yes
Patient preference study for different characteristics of systemic psoriasis treatments (Protimisis).	Rigopoulos et al., 2018	2018	Greece	Patients diagnosed moderate/severe plaque-type psoriasis for at least 1 year	310	18 choice sets 5 Attributes 2 Alternatives	Yes

Table 2 - 1: List of Discrete-Choice Experiment studies included in the systematic literature review of patient and physician preferences; including general characteristics of the studies.

Study	Author	Publication Year	Country	Subjects Included	Sample Size	DCE Design Characteristics	Industry funded
Patients' and Physicians' Preferences for Systemic Psoriasis Treatments: A Nationwide Comparative Discrete Choice Experiment (PsoCompare).	Schaarschmidt et al., 2018	2018	Germany	Patients with moderate to severe Psoriasis according to the criteria of the Committee for Medicinal Products for Human Use - Physicians	222 Patient 78 Physicians	24 choice sets 10 Attributes 2 Alternatives	No
Patient Preferences Associated with Therapies for Psoriatic Arthritis: A Conjoint Analysis.	Xu et al., 2018	2018	United States	Patients had to have at least 2 diagnoses of psoriatic arthritis	258 patients in Medicare plans 210 patients in commercial plans	10 choice sets 7 Attributes 2 Alternatives	Yes
Patient-Reported Outcomes are Important Elements of Psoriasis Treatment Decision Making: A Discrete Choice Experiment Survey of Dermatologists in the United States.	Feldman et al., 2019	2019	United States	Dermatologists or internists specializing in dermatology participating in clinical practice for at least 3 years	259	Not clear how many choice sets 6 Attributes 3 Alternatives	Yes
Patient preference for biologic treatments of psoriasis in Japan.	Tada et al., 2019	2019	Japan	Patients with self-reported diagnosis of psoriasis and currently receiving treatment	395	16 choice sets 6 Attributes 2 Alternatives	Yes

2.4.2. Quality assessment

Table 2-2 reports the quality assessment scores attributed to the DCE studies included. Using the PREFS checklist, it was determined that every study included in this review reported a clear purpose related to the identification of patient or physician preferences. Regarding the 'Respondents' aspect of the checklist, only two studies addressed the differences between responders and non-responders(44,54). Three studies reported strategies for increasing survey response rates however did not explicitly address differences between responders and non-responders(17,41,52). Most studies provided an adequate explanation of their methods (94%) and included appropriate statistical methods (96%), however only 74% of all studies reported all their findings transparently according to ISPOR recommendations. Common gaps in reporting findings were the lack of reporting all relevant coefficients, subgroup analysis scores or relative importance scores. To allow a more in-depth evaluation of the methodologies of each study, all four methodology-specific items from the ISPOR checklist were also assessed. Overall, studies clearly stated how the discrete-choice tasks were constructed (92%) and used appropriate methodologies to elicit preferences from their participants (98%). Of note, nearly a quarter of studies did not adequately justify the selection of the attributes and levels included in their study. Finally, only 56% of studies adequately justified the selection of the experimental design utilized (Appendix). With regards to final quality scores (whereas a score of 9 is considered the maximum), eight studies received a total score of 6 or lower, eight studies received a score between 6.1 and 7.5 and nine studies received a total quality score of 7.6-9 (Table 2-2).

Table 2 - 2: Quality assessment of the DCE studies included in the review according to both PREFS and ISPOR quality checklists

Study	PREFS					ISPOR Checklist				Final Score
	Purpose	Respondents	Explanation	Findings	Significance	Attributes and levels	Construction of tasks	Experimental Design	Preference Elicitation	
Ashcroft et al. 2006	1	0	1	0.5	1	0.5	1	0.5	1	6
Seston et al., 2007	1	0	1	0	1	1	1	0.5	1	6.5
Hauber et al., 2011	1	0	1	0.5	0	1	1	0	1	4.5
Schaarschmidt et al., 2011	1	0	1	1	1	0	1	0	1	6
Schmieder et al. 2012	1	0	1	1	1	0	1	0	1	6
Umar et al., 2012	1	0	1	1	1	1	1	0	0.5	6.5
Schaarschmidt et al., 2013	1	0	1	1	1	0	1	0	1	6
Umar et al., 2013	1	0	1	1	1	1	1	1	1	8
Torbica et al., 2014	1	0.5	1	0.5	1	1	1	1	1	8
Kauf et al., 2015	1	0	1	0.5	1	1	1	0.5	1	7
Kromer et al., 2015	1	0	1	1	1	1	1	1	1	8
Schaarschmidt et al., 2015	1	0	1	1	1	0.5	1	0.5	1	7
Rothery et al., 2016	1	0	1	0.5	1	1	1	1	1	7.5
Alcusky et al., 2017	1	0.5	1	1	1	1	1	1	1	8.5
Eliasson et al., 2017	1	0	1	1	1	1	1	1	1	5
Fairchild et al., 2017	1	0	1	0.5	1	1	1	0	1	6.5
Guevara et al., 2017	1	0	1	1	1	1	1	1	1	8
Gonzalez et al., 2017*	1	0	1	0.5	1	0	0	0.5	1	5
Kromer et al., 2017	1	0	1	1	1	1	1	1	1	8
Bolt et al., 2018	1	0.5	1	1	1	1	1	1	1	8.5
Rigopoulos et al., 2018	1	1	0	0	1	1	1	0.5	1	6.5
Schaarschmidt et al., 2018	1	0	1	1	1	1	1	1	1	8
Xu et al., 2018	1	0	0.5	1	1	0	1	0	1	5.5
Feldman et al., 2019	1	1	1	0.5	1	1	0	0	1	6.5
Tada et al., 2019	1	0	1	1	1	1	1	1	1	8
Total	25	3.5	23.5	18.5	24	19	23	14	24.5	
Percentage	100%	14%	94%	74%	96%	76%	92%	56%	98%	

Note: PREFS: Purpose, Respondents, Explanation, Findings, Significance; ISPOR: International Society for Pharmacoeconomics and Outcomes Research.

A more detailed analysis of key methodological considerations is represented in Table 2-3. When reporting on the specific methodology used to construct the DCE tasks and on deciding which attributes to include, all authors conducted a literature review or investigated relevant clinical evidence. Five studies referenced previous studies when reporting on how attributes were selected (22,38,49,51,53) and 96% of studies consulted experts within the field, (patients or clinicians with psoriasis knowledge). Interestingly, only 24% of studies reported to have pilot-tested their DCE.

2.4.3. Classification of attributes

The 25 DCE studies compiled a total of 191 attributes. 124 (65%) attributes were classified as outcome attributes, 55 (29%) as process attributes and 12 (6%) were cost related. Only five studies (20%) solely included outcome attributes(21,36,40,46,47). It should be noted that two of the outcome-only studies(21,40) considered plaque location an attribute, however in this analysis plaque location was not considered as an attribute, as the location was an independent variable in these studies. Eight studies (32%) included both outcome and process attributes(17,22,35,37,38,41,44,53) whereas twelve studies (48%) included outcome, process and cost attributes(5,20,39,42,43,45,48-52,54) (Appendix). Given the high level of variability in the attribute naming conventions used by researchers, this review bucketed the attributes into new categories (Appendix). Amongst all outcome attributes, 55% were efficacy-specific whereas 45% were safety specific. Efficacy-specific outcome measures were subdivided into 'Response Rate' (defined by probability of achieving an effect measured by Psoriasis Area Severity Index (PASI) or Body Surface Area (BSA) reduction – 53% of all efficacy attributes), 'Speed on Response' (defined by the time it takes to first experience relief of symptoms – 13% of all efficacy attributes), 'Response Maintenance or Sustainability' (defined by the longevity of the effect experienced by the patient – 25% of all efficacy attributes) and quality of life (defined by measures of health-related quality of life – 9% of all efficacy attributes). Safety-specific outcome measures were divided into mild adverse events (AE) (e.g., itching, nausea, vomiting etc. – 33% of all safety attributes), severe adverse events (e.g., risk of lymphoma, serious infections, melanoma or nonmelanoma skin cancer, etc. – 47% of all safety attributes) or adverse event management related attributes (defined as reversibility of AEs – 20% of all safety attributes).

Table 2 - 3: Quality assessment continued

Author	Literature/ Clinical Trials used to Attribute selection	Focus Groups used for attribute selection	Pilot-tested?	Attribute number	Visual representation of attribute	Sub-group analysis?
Ashcroft et al., 2006	Yes	Yes	No	6	No	No
Seston et al., 2007	Yes	Yes	No	6	No	No
Hauber et al., 2011	Yes	Yes	No	6	Yes	No
Schaarschmidt et al., 2011	Yes	Yes	No	11 (2groups)	No	Yes
Schmieder et al. 2012	Reference another study	Yes	No	11 (2groups)	no	Yes
Umar et al. 2012	Yes	Yes	No	11 (2groups)	No	Yes
Schaarschmidt et al., 2013	Reference another study	Yes	No	11 (2groups)	No	Yes
Umar et al., 2013	Yes	Yes	Yes	11 (2groups)	No	No
Torbica et al., 2014	Yes	Yes	Yes	5	no	Yes
Kauf et al., 2015	Yes	Yes	No	6	Yes	Yes
Kromer et al., 2015	Yes	Yes	No	11 (2groups)	No	Yes
Schaarschmidt et al., 2015	Reference another study	Yes	No	11 (2groups)	No	Yes
Rothery et al., 2016	Yes	Yes	No	3	No	No
Alcusky et al., 2017	Yes	Yes	No	7	Yes	No
Eliasson et al., 2017	Yes	Yes	Yes	6	Yes	Yes
Fairchild et al., 2017	Reference another study	Yes	No	5	Yes	No
Guevara et al., 2017	Yes	Yes	No	7	No	Yes
Kromer et al., 2017	Reference another study	Yes	No	5	No	Yes
Gonzalez et al., 2017	Yes	Yes	Yes	11	Yes	No
Bolt et al., 2018	Yes	Yes	Yes	7	yes	Yes
Rigopoulos et al., 2018	Yes	Yes	No	5	No	Yes
Schaarschmidt et al., 2018	Yes	Yes	Yes	10 (2groups)	No	Yes
Xu et al., 2018	Yes	No	No	7	No	No
Feldman et al., 2019	Yes	Yes	No	6	No	No
Tada et al., 2019	Yes	Yes	No	6	No	Yes
Total	100%	96%	24%	191 (average of 7.6/study)	28%	60%

Process attributes were identified using previously defined categories, namely mode of administration (21%), frequency (27%), location of treatment (20%), duration of treatment (14%), a combination of process attributes (9%) and other (9%). Five studies opted to combine multiple process attributes together, in most cases mode and frequency of administration(17,37,48,52,54). Lastly, cost attributes were defined as the specific cost to the patient (out-of-pocket costs) (Figure 2-2).

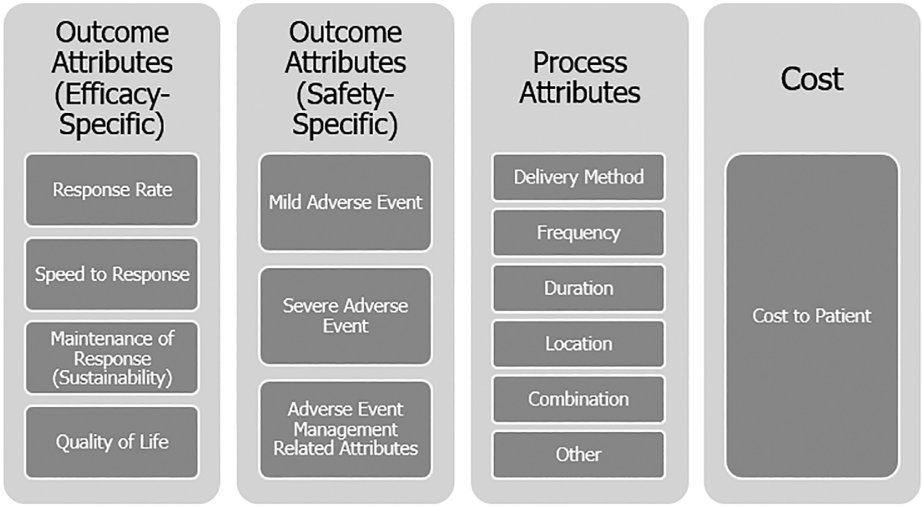


Figure 2 - 2: The final categorization of all the attributes included in the 25 DCE studies evaluated in this review.

2.4.4. Significance of attributes

Certain studies evaluated both patients and physicians or had participants identify preferences for different scenarios, and thus these iterations added to a larger study sample used in this review. In particular, the study by Alcusky et al., (17) asked both patients and physicians to elicit preferences for both moderate and severe hypothetical patient groups and thus provided four sets of 'most important' attributes. Also noteworthy, Xu et al.'s study (43) separated patients into commercially-insured and Medicare-covered groups, providing two data sets. Altogether we identified 32 'most important' attributes for patients and physicians and 32 'second most important' attributes. Only 17 studies (53%) reported relative importance scores (Table 2-4), for the remaining 15 data sets relative importance was calculated.

Table 2 - 4: Identification of the most and second most important attributes for each of the 25 studies included

Study	Category	Attribute Layout	Most Important Attribute (raw)	Most Important Attribute (categorized)	Second most important attribute (raw)	Second most important attribute (categorized)	Relative Importance included in study
Ashcroft et al. 2006	Physicians	Outcome Only	Time to moderate Improvement (weeks)	Response Speed	Risk of Skin Cancer	Serious Adverse Event	No
Seston et al., 2007	PSO Patients	Outcome Only	Time to moderate Improvement (weeks)	Response Speed	Risk of Skin Cancer	Serious Adverse Event	No
Hauber et al., 2011	PSO Patients	Process + Outcome + Cost	BSA affected after receiving treatment	Response Rate	Type of Treatment + Associated Experience	Process Attribute	No
Schaarschmidt et al., 2011	PSO Patients	Process + Outcome + Cost	Treatment Location	Process Attribute	Probability of Benefit	Response Rate	Yes
Schmieder et al. 2012	PSO Patients	Process + Outcome + Cost	Treatment Location	Process Attribute	Probability of Benefit	Response Rate	Yes
Umar et al., 2012	PSO Patients	Process + Outcome + Cost	Treatment Location	Process Attribute	Probability of Benefit	Response Rate	Yes
Schaarschmidt et al., 2013	PSO Patients	Process + Outcome + Cost	Treatment Location	Process Attribute	Probability of Benefit	Response Rate	Yes
Umar et al., 2013	PSO Patients	Process + Outcome + Cost	Treatment Location	Process Attribute	Probability of Benefit	Response Rate	Yes
Torbica et al., 2014	PSO Patients	Process + Outcome + Cost	Time Free of Symptoms	Response Maintenance	Reduced Life Expectancy	Severe Adverse Event	No

Table 2 - 4: Identification of the most and second most important attributes for each of the 25 studies included

Study	Category	Attribute Layout	Most Important Attribute (raw)	Most Important Attribute (categorized)	Second most important attribute (raw)	Second most important attribute (categorized)	Relative Importance included in study
Kauf et al., 2015*	PSO Patients	Outcome Only	BSA Covered by PSO (after treatment)	Response Rate	Risk of lymphoma	Serious Adverse Event	No
Kromer et al., 2015	PSO Patients	Process + Outcome	Risk of Severe AE	Serious Adverse Event	Probability of 90% improvement	Response Rate	Yes
Schaarschmidt et al., 2015	PSO Patients	Process + Outcome	Risk of Severe AE	Serious Adverse Event	Probability of 90% improvement	Response Rate	Yes
Rothery et al., 2016	PsA Patients	Outcome Only	Side effect of nausea or sickness from treatment	Mild Adverse Event	Health-related quality of life	Quality of life	No
Alcusky et al., 2017	Physicians (moderate PSO)	Process + Outcome	Dosing frequency and format	Process Attribute	Probability of Improvement (PASI)	Response Rate	Yes
Alcusky et al., 2017	Moderate PSO Patients	Process + Outcome	Dosing frequency and format	Process Attribute	Probability of Improvement (PASI)	Response Rate	Yes
Alcusky et al., 2017	Physicians (severe PSO)	Process + Outcome	Probability of Improvement (PASI)	Response Rate	Dosing frequency and format	Process Attribute	Yes
Alcusky et al., 2017	Severe PSO Patients	Process + Outcome	Probability of Improvement (PASI)	Response Rate	Probability that quality of life will improve	Quality of life	Yes
Eliasson et al., 2017	PSO Patients	Process + Outcome	Increased risk of serious infection	Serious Adverse Event	Increased Risk of melanoma or NMSC	Serious Adverse Event	No

Table 2 - 4: Identification of the most and second most important attributes for each of the 25 studies included

Study	Category	Attribute Layout	Most Important Attribute (raw)	Most Important Attribute (categorized)	Second most important attribute (raw)	Second most important attribute (categorized)	Relative Importance included in study
Fairchild et al., 2017	PSO Patients	Process + Outcome	% Body Surface Area	Response Rate	10-year mortality risk	Serious Adverse Event	No
Guevara et al., 2017	PSO Patients	Process + Outcome + Cost	Duration of Benefit	Response Maintenance	Frequency of Treatment	Process Attribute	Yes
Gonzalez et al., 2017	PSO Patients	Outcome Only	% BSA on Chest and Back	Response Rate	% BSA on Arms and Legs	Response Rate	No
Gonzalez et al., 2017	Physicians	Outcome Only	10-year Lymphoma Risk	Serious Adverse Event	% BSA on Arms and Legs	Response Rate	No
Kromer et al., 2017	PSO Patients	Process + Outcome	Probability of severe AE	Serious Adverse Event	Probability of 90% improvement	Response Rate	Yes
Bolt et al., 2018	PSO Patients	Process + Outcome	PASI 90%	Response Rate	Injection Type	Process Attribute	No
Bolt et al., 2018	Physicians	Process + Outcome	PASI 90%	Response Rate	Risk AE	Serious Adverse Event	No
Rigopoulos et al., 2018	PSO Patients	Process + Outcome + Cost	Onset of Action (in months)	Response Speed	Risk of SAEs	Serious Adverse Event	No
Schaarschmidt et al., 2018	Physicians	Process + Outcome + Cost	PASI 90 response	Response Rate	Probability of Severe AE	Serious Adverse Event	Yes
Schaarschmidt et al., 2018	PSO Patients	Process + Outcome + Cost	PASI 90 response	Response Rate	Probability of Mild AE	Mild Adverse Event	Yes

Table 2 - 4: Identification of the most and second most important attributes for each of the 25 studies included

Study	Category	Attribute Layout	Most Important Attribute (raw)	Most Important Attribute (categorized)	Second most important attribute (raw)	Second most important attribute (categorized)	Relative Importance included in study
Xu et al., 2018	Medicare PSO Patients	Process + Outcome + Cost	Route of Administration	Process Attribute	Improvement in daily tasks and activities	Quality of Life	No
Xu et al., 2018	Commercially insured PSO Patients	Process + Outcome + Cost	Cost to patients	Cost	Route of Administration	Process Attribute	No
Feldman et al., 2019	Physicians	Process + Outcome	Reduction in PASI (90%)	Response Rate	Combination of 3 patient-reported outcomes (itching/ performance of activities/ depression	Quality of Life	Yes
Tada et al., 2019	PSO Patients	Process + Outcome + Cost	Sustained efficacy after drug withdrawal	Response Maintenance	Dosing Convenience	Process Attribute	Yes

Note: PSO: psoriasis, AE: adverse event, NMSC: nonmelanoma skin cancer, BSA: body surface area.

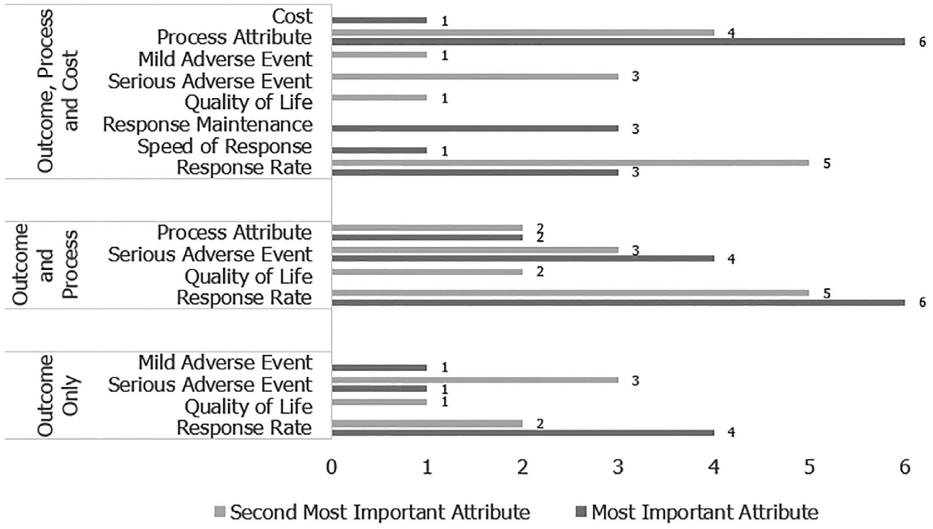


Figure 2 - 3: Identification of the most and second most important treatment attributes, differentiated by outcome only, outcome and process and outcome, process and cost studies.

To prevent cross-over between population-groups, we first evaluated all patient-specific preferences independently and then compared results with physician-specific preferences. Secondly, we also compared the distribution of preferences according to the included categories of attributes (i.e., outcome-only studies vs. process and outcome studies & process, outcome and cost studies). Results of our analysis are presented in Figure 2-3.

2.4.5. Patient versus physician preferences

In the patient sample (25 studies), efficacy-outcomes were identified as the most important attribute in twelve studies (48%), safety-outcomes in five studies (20%), process attributes in seven studies (28%) and cost only once (4%). Regarding the second most important attribute, efficacy was selected in thirteen studies (52%), safety in seven studies (28%) and process outcomes in five studies (20%). In the physician sample (N=7), efficacy was identified as the most important attribute 5 times (71%), whereas safety and process attributes were identified as most important in one study each (14% each). Regarding the second most important attribute, efficacy and safety were the second most important attributes in three studies respectively (43% each) whereas process attributes were only selected by physicians once (14%). Tallying the top two preferred attributes, efficacy was identified as the most important in 50% of patient-specific studies. Safety and process attributes were ranked as the top two most important attributes 12 times

each (24% each). The cost attribute was amongst the top two attributes only once. Similarly, in the physician sample, efficacy was identified within the top two most important attributes in 57% of the studies. However, safety (29%) appeared more among the top two attributes for physicians than process attributes (14%). Cost was never considered in the top two most significant attributes for physicians (Figure 2-3). Efficacy was revealed to be the most important treatment attribute for patients and physicians (Table 2-4).

2.4.6. Preferences by study design

In the outcome-only studies, efficacy was named the most important attribute in 66% of studies whereas safety only in 33%. Regarding the second most important attribute, there was an even split between efficacy and safety (50% each). In the outcome and process studies, we noticed an even split between the efficacy and safety attributes, both being evaluated as the most influential attribute in 50% of studies respectively. Regarding the second most important attributes, efficacy was identified as the second most important in 58% of studies, safety in 25% and process attributes in 17%. Lastly, when studies also included a cost element, only efficacy, process and cost attributes were identified by patients and physicians as being the most important attribute (50%, 43% and 7% of studies respectively). Regarding the second most important attributes, efficacy again ranked as the top second most preferred attribute being selected (43%), whereas safety and process attributes were selected in 29% of studies respectively (Figure 2-3). The exact attributes identified as most important are listed in Table 2-4.

2.4.7. Subgroup preference trends

Overall, 15 out of 25 (60%) studies included subgroup analyses. Regarding age, three significant associations were identified. Firstly, older participants have been reported to attach less importance to response rates (treatment efficacy) than younger participants(20,35,42,50,52). Secondly, older patients are more influenced by the risk of severe AEs than younger participants(35,42,45,50,52,53). Lastly, older patients seem to be less concerned with the speed of response in comparison to younger participants(35,52,53). In regards to marital status, two studies identified that patients who identified themselves as single placed more importance on response rates compared to participants in a relationship(35,50). In terms of disease severity, two studies identified that patients with more severe psoriasis were more tolerant to severe AEs than those participants with milder forms of psoriasis(41,42). Also, three studies identified that patients who have more experience with their condition (years since diagnosis) were less concerned with response rates in comparison to those who have not lived as long with psoriasis(37,42,51). In terms

of the impact of psoriasis on participants' quality of life, as measured by the Dermatology Life Quality Index (DLQI), two studies identified that patients with greater DLQI scores (equivalent to greater impact of psoriasis on quality of life) placed less value on treatment efficacy(35,37), whereas two studies demonstrated that patients with higher DLQI scores placed more value on response maintenance than those with lower DLQI scores(35,52). Lastly, patients who were also diagnosed with PsA were less concerned with speed to response(22,42) and they were more concerned with both response rates and response maintenance than patients without this comorbidity(22,49).

2.5. Discussion

This study confirmed that DCE methodology is being used more frequently to capture preferences regarding treatment characteristics(55). Despite increased adoption of DCE methodology, this study has identified that the current body of literature provides a limited understanding of patient preferences in PsA and should focus on conducting more direct comparisons of the preferences between patients and physicians. The usefulness of these studies are widely recognized, by example earlier this year (February, 2019), NICE provided its first recommendations regarding the design of patient preference studies and have encouraged authors to seek consultation and feedback(56). As patient preference insights increasingly inform regulatory and reimbursement processes of new medication applications in both North-America(57,58) and Europe(59,60), the quality of DCE studies must improve so that the findings drawn from these studies are reliable and transferred to decision-making contexts(19).

To meet necessary quality standards, this review identified specific gaps intrinsic to the methodology adopted by current DCE studies, specifically in the context of capturing PSO preferences. A major gap in the current DCE literature is the lack of reporting on non-responders. Though it is admittedly difficult to gather information on participants that do not respond, careful survey construction can both attract higher response rates and can ensure that the responses truly reflect the preferences of respondents in real-world settings and are thus more generalizable. According to Bridges et al.(31), interviewer-led administration of surveys may improve a respondent's comprehension of the DCE exercise. Secondly, confirming the results of an evaluation conducted by ISPOR in 2012(61) which determined that the experimental design of most studies was not being properly documented, a quarter of studies evaluated in this review did not adequately report the findings of their statistical analysis. Studies either omit reporting coefficient

scores for all attributes or simply interpreted coefficient scores without considering the range of the levels. Applying the range method as described by Hauber et al. (34), was complicated by the heterogeneity of data reporting styles. We therefore recommend that authors either report relative importance scores or are transparent in the use of coefficients for reporting the importance of attributes evaluated.

Although studies have improved in reporting the experimental design used in the last four years, scientific gaps remain. Specifically, the selection of specific experimental design was seldom justified, and these designs were piloted in only a fifth of all studies reviewed. DCE tasks are known to be cognitively burdensome, and thus overcrowding of choices can complicate decision-making(41,62). This review identified that the number of attributes included has decreased in the last four years to comply according to ISPOR recommendations, however as the average number of attributes remains high, we echo these recommendations to try to minimize the overcrowding of attributes in DCE design. A further possibility to avoid information overload due to too many attributes is to divide the attributes into groups. The DCEs by Schaarschmidt et al., Schmieder et al., Umar et al. and Kromer et al. contained 10 or 11 attributes. However, the attributes were divided into two groups with 5-6 attributes each in order to reduce the number of attributes presented in parallel, with one attribute being part of both groups to enable a later comparison; similar examples of combining treatment attributes can be found (Appendix). Lastly, given the vast heterogeneity in attribute naming conventions we have proposed strategic categorization of attributes for psoriasis. Outcome attributes can be firstly differentiated into efficacy and safety-specific outcomes; these should then be further sub-categorized to allow to address the full range of preferences for treatment options. We caution that although categorization may improve alignment and comparisons amongst studies, it may also take away from gaining insights into the intricacies of patient and physician preferences.

Our study has confirmed the findings of previous reviews(9,23), efficacy tends to be the most influential treatment attribute for both patients and physicians. We use the term efficacy broadly here to include response rate, speed of response, response maintenance and quality of life measures. All these sub-categories were identified as being within the top two most influential treatment attributes for treatment selection. For psoriasis, the current standard measure for treatment efficacy is PASI90(63). However, it was demonstrated in some studies that patients may place more value to full clearance, especially in comparison to physicians(21,38,48). For this reason, we recommend that future studies assess the difference in relative importance between PASI90 and PASI100. Furthermore, this finding has greater

implications for future clinical studies and for pricing and reimbursement decisions that aim to make value-based decisions that closely reflect patient preferences. Another interesting finding reported by Tada et al. (45) was that patients placed most value on the sustainability of efficacy after treatment withdrawal, in which another study termed this attribute “bio-holiday” potential(41). We acknowledge that though it may be very difficult to measure this end-point pre-marketing authorization, it currently represents an unmet patient-need that may provide opportunities for future investigation. This further supports the integration of real-world evidence and post-approval clinical evidence in value-based decision-making at a regulatory level.

Safety attributes were also considered important in treatment decision-making by both patients and physicians. As highlighted in previous reviews(9,23), severe AEs had a stronger influence on decision-making than mild AEs. Specifically, 10-year risk of tuberculosis, lymphoma and of serious infections are of primary concern to both patients and physicians when selecting appropriate treatments. According to our assessment, in comparison to patients, physicians identified severe AEs as more influential in treatment decision-making. Additionally, sub-group analysis of physicians identified more experienced physicians tend to place more weight and consideration to severe AE profiles when selecting which treatment to prescribe(41,42). Conversely to physicians, our results demonstrate that patients place great importance on process attributes. In fact, patients selected various process attributes as being the most important attribute influencing decision-making in more studies than adverse events (mild and severe) altogether, especially when studies included a cost element. This not only suggests that procedural should be incorporated into decision-making considerations at the regulatory level, it also suggests that there is a lack of congruence between physicians and patients. Finding alignment between physicians and patients can lead to patient-centric prescribing and can shift the focus on driving patient-value(64). In turn, improved alignment through shared decision-making has been shown to positively affect treatment outcomes through increase adherence rates(65). The results of this review can stimulate communication of preferences between patients and physicians. The most important attributes identified in this review can potentially be integrated into patient-decision aids, which have also been shown to be effective at increasing patient’s knowledge and satisfaction(66).

Lastly, given that patient and physician preferences are indeed heterogenous, participant subgroups must be distinguished in order to allow regulators the opportunity to adapt their decisions to the appropriate population groups in

question(19). The current review only briefly addresses the subgroup analysis performed by the studies included, however in doing so we were able to identify that there is significant variability in the preferences of patient subgroups. Of note, age, disease severity and quality of life impact (as measured by the DLQI) are significant observable characteristics that clinicians should consider when deciding upon the best treatment course.

This review includes certain limitations that are worth mentioning. Firstly, our review complemented the PREFS checklist with four items from the ISPOR checklist. In doing so, we did not adequately evaluate the data-collection plan and statistical analysis executed in the studies included. As noted above, we highlighted gaps in the reporting of results in certain studies. Thus, a more in-depth analysis could have unearthed more limitations in the results reported. Furthermore, it is important to note that using the range method to quantify the relative importance of attributes is highly dependent on the range of levels chosen to define any given attribute. This emphasizes the importance of setting realistic (clinically relevant) levels for each attribute identified. Another limitation of this study is that although we consulted with an expert in the field of psoriasis to assist with the categorization of all attributes, it is possible that other authors may opt to categorize attributes using language more consistent with their local context. This study does however provide transparency regarding the categorization process executed (Appendix). Lastly, this study decided to occlude conference publications from this review. However, 12 conference abstracts were identified that evaluated patient-preferences in a DCE format. This again points to the growing relevance of DCE studies as being a preferred method to study patient preferences, but it also highlights the importance of updating the results of this review once new evidence becomes available.

2.6. Conclusions

In this systematic review of DCEs investigating physician and patient preferences for psoriasis treatment, it was determined that both patient and physicians place the greatest level of importance on efficacy-specific outcome measures such as response rates (especially PASI 90) when making decisions regarding treatment choice. In general, efficacy, safety and process attributes were all deemed important by patients and physicians, whereas physicians placed more weight on safety attributes and patients on process attributes. To facilitate shared decision-making, clinicians must take into consideration diverse treatment attributes and become accustomed to individual variability in preferences. The highly important attributes identified in this review can serve to design patient-decision aids and may provide

clinicians with the starting point to facilitate these conversations. Lastly our review confirms that process attributes in addition to efficacy and safety attributes deserve further consideration at the regulatory level.

2.7. References

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. Journal of Investigative Dermatology 2013;133:377-385.
2. Griffiths CEM, van der Walt JM, Ashcroft DM et al. The global state of psoriasis disease epidemiology: a workshop report. Br J Dermatol 2017;177:e4-e7.
3. Bhosle MJ, Kulkarni A, Feldman SR, Balkrishnan R. Quality of life in patients with psoriasis. Health Qual Life Outcomes 2006;4:35.
4. de Arruda LH, De Moraes AP. The impact of psoriasis on quality of life. Br J Dermatol 2001;144 Suppl 58:33-6.
5. Umar N, Schaarschmidt M, Schmieder A, Peitsch WK, Schollgen I, Terris DD. Matching physicians' treatment recommendations to patients' treatment preferences is associated with improvement in treatment satisfaction. J Eur Acad Dermatol Venereol 2013;27:763-70.
6. Thorneloe RJ, Bundy C, Griffiths CE, Ashcroft DM, Cordingley L. Nonadherence to psoriasis medication as an outcome of limited coping resources and conflicting goals: findings from a qualitative interview study with people with psoriasis. Br J Dermatol 2017;176:667-676.
7. Jevtic T, Bukumiric Z, Jankovic SM. Effects of treatment adherence on clinical and economic outcomes in patients with psoriasis. Med Glas (Zenica) 2013;10:106-12.
8. Kitchen H, Cordingley L, Young H, Griffiths CE, Bundy C. Patient-reported outcome measures in psoriasis: the good, the bad and the missing! Br J Dermatol 2015;172:1210-21.
9. Florek AG, Wang CJ, Armstrong AW. Treatment preferences and treatment satisfaction among psoriasis patients: a systematic review. Arch Dermatol Res 2018;310:271-319.
10. Bridges J, Onukwugha E, Johnson F, Hauber A. Patient preference methods—a patient centered evaluation paradigm. ISPOR connections 2007;13:4-7.
11. Bolt T, Mahlich J, Nakamura Y, Nakayama M. Hematologists' Preferences for First-line Therapy Characteristics for Multiple Myeloma in Japan: Attribute Rating and Discrete Choice Experiment. Clin Ther 2018;40:296-308.e2.
12. Ho MP, Gonzalez JM, Lerner HP et al. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc 2015;29:2984-93.
13. Underwood G. NICE to research patient preferences in HTA. 2016.
14. van Overbeeke E, Whichello C, Janssens R et al. Factors and situations influencing the value of patient preference studies along the medical product lifecycle: a literature review. Drug Discov Today 2019;24:57-68.
15. Mangham LJ, Hanson K, McPake B. How to do (or not to do) ... Designing a discrete choice experiment for application in a low-income country. Health Policy Plan 2009;24:151-8.
16. Ryan M, Farrar S. Using conjoint analysis to elicit preferences for health care. Bmj 2000;320:1530-3.
17. Alcusky M, Lee S, Lau G et al. Dermatologist and Patient Preferences in Choosing Treatments for Moderate to Severe Psoriasis. Dermatol Ther (Heidelb) 2017;7:463-483.
18. Reed SD, Lavezzari G. International Experiences in Quantitative Benefit-Risk Analysis to Support Regulatory Decisions. Value Health 2016;19:727-729.

19. Vass CM, Payne K. Using discrete choice experiments to inform the benefit-risk assessment of medicines: are we ready yet? Pharmacoeconomics 2017;35:859-866.
20. Schaarschmidt M-L, Schmieder A, Umar N et al. Patient preferences for psoriasis treatments: process characteristics can outweigh outcome attributes. Archives of dermatology 2011;147:1285-1294.
21. Kauf TL, Yang J-C, Kimball AB et al. Psoriasis patients' willingness to accept side-effect risks for improved treatment efficacy. Journal of Dermatological Treatment 2015;26:507-513.
22. Schaarschmidt M-L, Kromer C, Herr R et al. Patient preferences for biologicals in psoriasis: top priority of safety for cardiovascular patients. PloS one 2015;10:e0144335.
23. Gonzalez JM. Evaluating risk tolerance from a systematic review of preferences: the case of patients with psoriasis. The Patient-Patient-Centered Outcomes Research 2018;11:285-300.
24. Fink A. Conducting research literature reviews: from the Internet to paper: Sage Publications, 2019.
25. Yu T, Enkh-Amgalan N, Zorigt G. Methods to perform systematic reviews of patient preferences: a literature survey. BMC medical research methodology 2017;17:166.
26. Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS medicine 2009;6:e1000100.
27. Umar N, Yamamoto S, Loerbroks A, Terris D. Elicitation and use of patients' preferences in the treatment of psoriasis: a systematic review. Acta dermato-venereologica 2012;92:341-347.
28. Kleij K-S, Tangermann U, Amelung VE, Krauth C. Patients' preferences for primary health care–a systematic literature review of discrete choice experiments. BMC health services research 2017;17:476.
29. Papaioannou D, Sutton A, Carroll C, Booth A, Wong R. Literature searching for social science systematic reviews: consideration of a range of search techniques. Health Information & Libraries Journal 2010;27:114-122.
30. Cuchacovich R, Perez-Alamino R, Garcia-Valladares I, Espinoza LR. Steps in the management of psoriatic arthritis: a guide for clinicians. Ther Adv Chronic Dis 2012;3:259-269.
31. Bridges JF, Hauber AB, Marshall D et al. Conjoint analysis applications in health—a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value in health 2011;14:403-413.
32. Reed Johnson F, Lancsar E, Marshall D et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health 2013;16:3-13.
33. Joy SM, Little E, Maruthur NM, Purnell TS, Bridges JF. Patient preferences for the treatment of type 2 diabetes: a scoping review. Pharmacoeconomics 2013;31:877-892.
34. Hauber AB, González JM, Groothuis-Oudshoorn CG et al. Statistical methods for the analysis of discrete choice experiments: a report of the ISPOR Conjoint Analysis Good Research Practices Task Force. Value in health 2016;19:300-315.

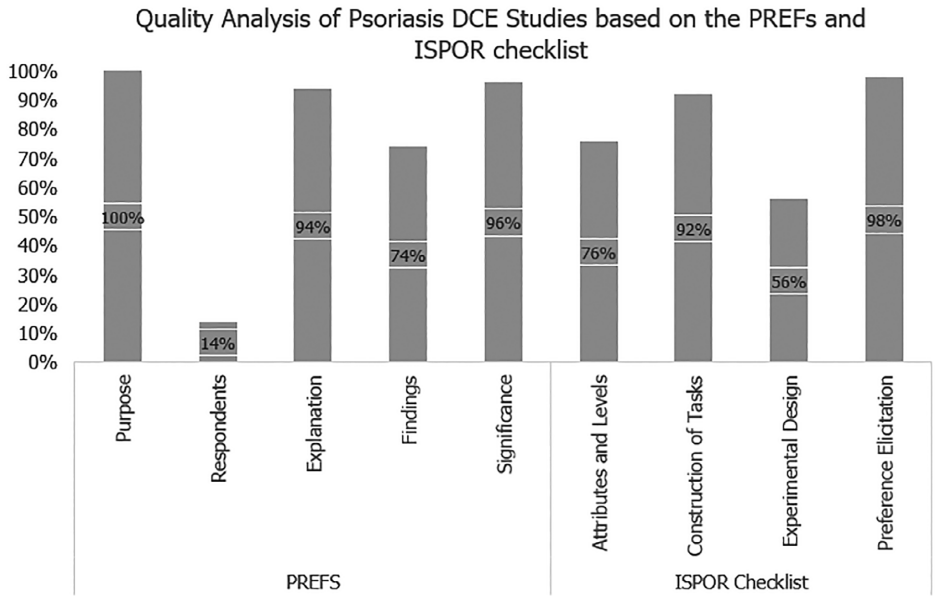
35. Kromer C, Schaarschmidt M-L, Schmieder A, Herr R, Goerdt S, Peitsch WK. Patient preferences for treatment of psoriasis with biologicals: a discrete choice experiment. PloS one 2015;10:e0129120.
36. Rothery C, Bojke L, Richardson G et al. A discrete choice experiment to explore patients' willingness to risk disease relapse from treatment withdrawal in psoriatic arthritis. Clinical rheumatology 2016;35:2967-2974.
37. Eliasson L, Bewley AP, Mughal F et al. Evaluation of psoriasis patients' attitudes toward benefit–Risk and therapeutic trade-offs in their choice of treatments. Patient preference and adherence 2017;11:353.
38. Fairchild AO, Reed SD, Johnson FR, Anglin G, Wolka AM, Noel RA. What is clearance worth? Patients' stated risk tolerance for psoriasis treatments. Journal of Dermatological Treatment 2017;28:709-715.
39. Guevara B, Gonzales N, Visitacion L. patient preference on psoriasis treatment in a Philippine Tertiary Hospital: a conjoint analysis: P127. Journal of the European Academy of Dermatology & Venereology 2016;30:62.
40. Gonzalez J, Johnson F, McAteer H, Posner J, Mughal F. Comparing preferences for outcomes of psoriasis treatments among patients and dermatologists in the UK: results from a discrete-choice experiment. British Journal of Dermatology 2017;176:777-785.
41. Bolt T, Kobayashi H, Mahlich J. Patient and Physician Preferences for Therapy Characteristics for Psoriasis: A Discrete Choice Experiment in Japan. PharmacoEconomics-open 2018:1-10.
42. Schaarschmidt M-L, Herr R, Gutknecht M et al. Patients' and Physicians' Preferences for Systemic Psoriasis Treatments: A Nationwide Comparative Discrete Choice Experiment (PsoCompare). Acta dermato-venereologica 2018;98:200-205.
43. Xu Y, Sudharshan L, Hsu M-A et al. Patient preferences associated with therapies for psoriatic arthritis: a conjoint analysis. American health & drug benefits 2018;11:408.
44. Feldman SR, Regnier SA, Chirilov A, Hey F, Gilloteau I, Cella D. Patient-Reported Outcomes are Important Elements of Psoriasis Treatment Decision Making: A Discrete Choice Experiment Survey of Dermatologists in the United States. Journal of the American Academy of Dermatology 2019.
45. Tada Y, Ishii K, Kimura J, Hanada K, Kawaguchi I. Patient preference for biologic treatments of psoriasis in Japan. The Journal of dermatology 2019.
46. Ashcroft D, Seston E, Griffiths C. Trade-offs between the benefits and risks of drug treatment for psoriasis: a discrete choice experiment with UK dermatologists. British Journal of Dermatology 2006;155:1236-1241.
47. Seston EM, Ashcroft DM, Griffiths CE. Balancing the benefits and risks of drug treatment: a stated-preference, discrete choice experiment with patients with psoriasis. Archives of dermatology 2007;143:1175-1179.
48. Hauber AB, Gonzalez JM, Schenkel B, Lofland JH, Martin S. The value to patients of reducing lesion severity in plaque psoriasis. Journal of Dermatological Treatment 2011;22:266-275.
49. Schmieder A, Schaarschmidt M-L, Umar N et al. Comorbidities significantly impact patients' preferences for psoriasis treatments. Journal of the American Academy of Dermatology 2012;67:363-372.

50. Umar N, Schöllgen I, Terris DD. It is not always about gains: utilities and disutilities associated with treatment features in patients with moderate-to-severe psoriasis. Patient preference and adherence 2012;6:187.
51. Schaarschmidt ML, Umar N, Schmieder A et al. Patient preferences for psoriasis treatments: impact of treatment experience. Journal of the European Academy of Dermatology and Venereology 2013;27:187-198.
52. Torbica A, Fattore G, Ayala F. Eliciting preferences to inform patient-centred policies: the case of psoriasis. Pharmacoeconomics 2014;32:209-223.
53. Kromer C, Peitsch WK, Herr R, Schmieder A, Sonntag D, Schaarschmidt ML. Treatment preferences for biologicals in psoriasis: experienced patients appreciate sustainability. JDDG: Journal der Deutschen Dermatologischen Gesellschaft 2017;15:189-200.
54. Rigopoulos D, Ioannides D, Chaidemenos G et al. Patient preference study for different characteristics of systemic psoriasis treatments (Protimisis). Dermatologic therapy 2018;31:e12592.
55. Bien DR, Danner M, Vennedey V, Civello D, Evers SM, Hiligsmann M. Patients' Preferences for Outcome, Process and Cost Attributes in Cancer Treatment: A Systematic Review of Discrete Choice Experiments. Patient 2017;10:553-565.
56. National Institute for Health and Care Excellence. NICE provides first scientific advice on patient preference study design. 2019.
57. Johnson FR, Zhou M. Patient preferences in regulatory benefit-risk assessments: a US perspective. Value in Health 2016;19:741-745.
58. Klein AV, Hardy S, Lim R, Marshall DA. Regulatory decision making in Canada—exploring new frontiers in patient involvement. Value in Health 2016;19:730-733.
59. Mott DJ. Incorporating Quantitative Patient Preference Data into Healthcare Decision Making Processes: Is HTA Falling Behind? : Springer, 2018.
60. Mühlbacher AC, Juhnke C, Beyer AR, Garner S. Patient-focused benefit-risk analysis to inform regulatory decisions: the European Union perspective. Value in Health 2016;19:734-740.
61. Johnson FR, Lancsar E, Marshall D et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR conjoint analysis experimental design good research practices task force. Value in Health 2013;16:3-13.
62. Addelman S. Symmetrical and asymmetrical fractional factorial plans. Technometrics 1962;4:47-58.
63. Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. Journal of the European Academy of Dermatology and Venereology : JEADV 2015;29:645-8.
64. Mühlbacher AC, Juhnke C. Patient preferences versus physicians' judgement: does it make a difference in healthcare decision making? Applied health economics and health policy 2013;11:163-180.
65. Wilson SR, Strub P, Buist AS et al. Shared treatment decision making improves adherence and outcomes in poorly controlled asthma. American journal of respiratory and critical care medicine 2010;181:566-577.
66. Stacey D, Légaré F, Lewis K et al. Decision aids for people facing health treatment or screening decisions. Cochrane Database of Systematic Reviews 2017.

2.8. Appendix

Appendix Table 2 - 1: Frequency of general characteristics of studies included by category

Characteristic:	Category:	Number of Studies (N)	Percentage of total study sample
Country	Germany	9	36%
	Greece	1	4%
	Italy	1	4%
	Japan	2	8%
	Philippines	1	4%
	United Kingdom	5	20%
	United States	6	24%
Publication Year	2000-2004	0	0%
	2005-2009	2	8%
	2010-2014	7	28%
	2015-2017	10	40%
	2018-Current	6	24%
Target Population	All Psoriasis Patients	6	24%
	Moderate to Severe Psoriasis Patients	11	44%
	Psoriatic Arthritis Patients	2	8%
	Dermatologists and Physicians (only)	2	8%
	Both Patients and Physicians	4	16%
Population Sample Size – Physician-Studies	0-150	2	33%
	151-300	4	67%
	301+	0	0%
Population Sample Size – Patient-Studies	0-150	4	17%
	151-300	12	52%
	301+	7	30%



Appendix Figure 2-1: Quality overview of all the DCE studies included. This graph denotes the percentage of studies that achieved an acceptable score (score = 1) in each of the PREFS and ISPOR checklist items.
Note: DCE: Discrete-Choice Experiment. PREFS: Purpose, Respondents, Explanation, Findings, Significance; ISPOR: International Society for Pharmacoeconomics and Outcomes Research.

Appendix Table 2 - 2: The distribution of all attributes by category for each of the 25 DCE studies included in this review

References	Attributes (total)	Outcome	Process	Cost	Outcome Efficacy				
					Quality of Life	Speed of Response	Response Rate	Maintenance of Response (Sustainability)	
Ashcroft et al., 2006	6	6	0	0	0	1	0	1	
Seston et al., 2007	6	6	0	0	0	1	0	1	
Hauber et al., 2011	6	3	2	1	0	0	2	0	
Schaarschmidt et al., 2011	11	6	4	1	0	0	2	1	
Schmieder et al. 2012	11	6	4	1	0	0	2	1	
Umar et al.. 2012	11	6	4	1	0	0	2	1	
Schaarschmidt et al., 2013	11	6	4	1	0	0	2	1	
Umar et al., 2013	11	6	4	1	0	0	2	1	
Torbica et al., 2014	5	3	1	1	0	1	0	1	
Kauf et al., 2015	6	5	1	0	0	0	2	0	
Kromer et al., 2015	11	7	4	0	0	1	3	1	
Schaarschmidt et al., 2015	11	7	4	0	0	1	3	1	
Rothery et al., 2016	3	3	0	0	1	0	0	1	
Alcusky et al., 2017	7	5	2	0	1	0	1	1	
Eliasson et al., 2017	6	5	1	0	0	0	1	0	
Fairchild et al., 2017	5	4	1	0	0	0	2	0	

	Outcome Safety			Process						Cost
	Serious Adverse Event	Mild Adverse Event	Adverse Event Manag-ement	Location	Frequency	Dura-tion	Delivery Method	Combi-nation	Other	
	2	2	0	0	0	0	0	0	0	0
	2	2	0	0	0	0	0	0	0	0
	1	0	0	0	0	0	0	1	1	1
	0	1	2	1	1	1	1	0	0	1
	0	1	2	1	1	1	1	0	0	1
	0	1	2	1	1	1	1	0	0	1
	0	1	2	1	1	1	1	0	0	1
	0	1	2	1	1	1	1	0	0	1
	1	0	0	0	0	0	0	1	0	1
	3	0	0	0	0	0	0	0	1	0
	1	1	0	1	1	1	1	0	0	0
	1	1	0	1	1	1	1	0	0	0
	0	1	0	0	0	0	0	0	0	0
	1	1	0	0	0	0	0	1	1	0
	3	1	0	0	0	0	0	1	0	0
	2	0	0	0	1	0	0	0	0	0

Appendix Table 2 - 2: The distribution of all attributes by category for each of the 25 DCE studies included in this review

References	Attributes (total)	Outcome	Process	Cost	Outcome Efficacy			
					Quality of Life	Speed of Response	Response Rate	Maintenance of Response (Sustainability)
Guevara et al., 2017	7	3	3	1	0	0	1	1
Gonzalez et al., 2017	5	4	1	0	0	0	1	0
Kromer et al., 2017	11	7	4	0	0	1	3	1
Bolt et al., 2018	7	4	3	0	0	0	1	1
Rigopoulos et al., 2018	5	3	1	1	0	1	0	1
Schaarschmidt et al., 2018	10	5	4	1	0	1	2	0
Xu et al., 2018	7	4	2	1	1	0	2	0
Feldman et al., 2019	6	5	1	0	3	0	1	0
Tada et al., 2019	6	4	1	1	0	1	1	1
Total	191	123	56	12	6	9	36	17
Percentage:	100%	64,4%	29,3%	6,3%	8,8%	13,2%	52,9%	25,0%

	Outcome Safety			Process						Cost
	Serious Adverse Event	Mild Adverse Event	Adverse Event Manag-ement	Location	Frequency	Dura-tion	Delivery Method	Combi-nation	Other	
	0	1	0	1	1	0	1	0	0	1
	3	0	0	0	0	0	0	0	1	0
	1	1	0	1	1	1	1	0	0	0
	1	0	1	1	1	0	1	0	0	0
	1	0	0	0	0	0	0	1	0	1
	1	1	0	1	1	0	1	0	1	1
	1	0	0	0	1	0	1	0	0	1
	0	1	0	0	1	0	0	0	0	0
	1	0	0	0	1	0	0	0	0	1
	26	18	11	11	15	8	12	5	5	12
	47,3%	32,7%	20,0%	19,6%	26,8%	14,3%	21,4%	8,9%	8,9%	10%

Appendix Table 2 - 3: All efficacy-specific outcome attributes extracted from all 25 DCE studies.

Outcome Attribute (Efficacy-Specific)	Final Categorization	Author	Study Count
Probability that dermatology life quality index (DLQI) score will improve 16 weeks after treatment initiation	Quality of Life	Alcusky et al., 2017	1
Improvement in the ability to perform daily activities	Quality of Life	Xu et al., 2018; Feldman et al., 2019	2
Health-related quality of life	Quality of Life	Rothery et al., 2016	1
Time to relapse	Response Maintenance	Ashcroft et al., 2006; Seston et al., 2007	2
Duration of benefit	Response Maintenance	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013; Guevara et al., 2017; Rigopoulos et al., 2018	7
Sustainability of therapeutic success	Response Maintenance	Kromer et al., 2015; Schaarschmidt et al., 2015; Kromer et al., 2017; Tada et al., 2019	4
Risk of relapse	Response Maintenance	Rothery et al., 2016	1
Probability of loss of response within 1 year	Response Maintenance	Alcusky et al., 2017	1
Probability of stopping therapy within 1 year for non-efficacy reasons	Response Maintenance	Alcusky et al., 2017	1
Stop rate for treatment (percentage of patients not completing treatment)	Response Maintenance	Bolt et al., 2018	1
Bio-holiday availability (6-month break in treatment without worsening of symptoms)	Response Maintenance	Bolt et al., 2018	1
Severity (color, inflammation, and texture) of psoriasis lesions after treatment	Response Rate	Hauber et al., 2011	1

Appendix Table 2 - 3: All efficacy-specific outcome attributes extracted from all 25 DCE studies.

Outcome Attribute (Efficacy-Specific)	Final Categorization	Author	Study Count
Magnitude of benefit	Response Rate	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013; Guevara et al., 2017	6
Time free of symptoms	Response Rate	Torbica et al., 2014	1
Ability to reduce daily joint pain and swelling	Response Rate	Xu et al., 2018	1
Patients who achieve clear or almost clear skin	Response Rate	Xu et al., 2018	1
Percentage of patients who achieved complete relief of itching	Response Rate	Feldman et al., 2019	1
Percentage of patients whose depression resolved	Response Rate	Feldman et al., 2019	1
Time to achieve moderate (50%) improvement	Response Rate	Ashcroft et al., 2006; Seston et al., 2007; Torbica et al., 2014	3
Percentage of body surface area (BSA) covered by lesions after treatment	Response Rate	Hauber et al., 2011	1
Probability of benefit	Response Rate	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013	5
Severity of psoriasis plaques described with photographs	Response Rate	Kauf et al., 2015; Gonzalez et al., 2017	2
Amount of body surface area (BSA) covered	Response Rate	Kauf et al., 2015	1
Probability of 50% improvement	Response Rate	Kromer et al., 2015; Schaarschmidt et al., 2015; Kromer et al., 2017	3
Probability of 90% improvement	Response Rate	Kromer et al., 2015; Schaarschmidt et al., 2015; Kromer et al., 2017; Bolt et al., 2018; Schaarschmidt et al., 2018; Feldman et al., 2019	7

Appendix Table 2 - 3: All efficacy-specific outcome attributes extracted from all 25 DCE studies.

Outcome Attribute (Efficacy-Specific)	Final Categorization	Author	Study Count
Probability of improvement in psoriasis plaques as measured by the psoriasis area severity index (PASI) and percentage of body surface area (BSA) that remains affected 16 weeks after treatment initiation	Response Rate	Alcusky et al., 2017	1
Efficacy	Response Rate	Eliasson et al., 2017	1
Severity of plaque lesions	Response Rate	Fairchild et al., 2017	1
Percentage of body, face or hands area affected	Response Rate	Fairchild et al., 2017	1
Probability of psoriasis area severity index (PASI)	Response Rate	Schaarschmidt et al., 2018; Feldman et al., 2019	2
Probability of American College of Rheumatology 20% response criteria (ACR20)	Response Rate	Kromer et al., 2015; Schaarschmidt et al., 2015; Kromer et al., 2017	4
Location (chest + back + either legs or arms)	Secondary Characteristic	Kauf et al., 2015; Gonzalez et al., 2017	2
Time until response	Speed of Response	Kromer et al., 2015; Schaarschmidt et al., 2015; Kromer et al., 2017; Rigopoulos et al., 2018; Schaarschmidt et al., 2018	5
Early onset of efficacy	Speed of Response	Tada et al., 2019	1

Appendix Table 2 - 4: All Safety-specific outcome attributes extracted from all 25 DCE studies

Outcome Attribute (Safety-Specific)	Final Categorization	Author	Study Count
Probability of adverse events (AE)	Mild adverse event	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013; Guevara et al., 2017	6
Risk of skin irritation	Mild adverse event	Ashcroft et al., 2006; Seston et al., 2007	2
Probability of mild adverse events (AE)	Mild adverse event	Kromer et al., 2015; Schaarschmidt et al., 2015; Alcusky et al., 2017; Kromer et al., 2017; Schaarschmidt et al., 2018	5
Side effects of nausea or sickness from treatment	Mild adverse event	Rothery et al., 2016; Eliasson et al., 2017	2
Risk of high blood pressure	Severe adverse event	Ashcroft et al., 2006; Seston et al., 2007	2
Probability of severe adverse event	Severe adverse event	Kromer et al., 2015; Schaarschmidt et al., 2015; Alcusky et al., 2017; Kromer et al., 2017; Bolt et al., 2018; Rigopoulos et al., 2018; Schaarschmidt et al., 2018	7
20-year risk of skin cancer	Severe adverse event	Ashcroft et al., 2006; Seston et al., 2007	2
Risk of serious lung infection	Severe adverse event	Hauber et al., 2011; Eliasson et al., 2017; Xu et al., 2018; Tada et al., 2019	4
Reduced life expectancy	Severe adverse event	Torbica et al., 2014	1
10-year risks of tuberculosis	Severe adverse event	Kauf et al., 2015; Eliasson et al., 2017; Fairchild et al., 2017; Gonzalez et al.; 2017	4
10-year serious infection risk	Severe adverse event	Kauf et al., 2015; Fairchild et al., 2017; Gonzalez et al.; 2017	3
10-year lymphoma risk	Severe adverse event	Kauf et al., 2015; Gonzalez et al.; 2017	2
Long-term risk of melanoma or nonmela-noma skin cancer	Severe adverse event	Eliasson et al., 2017	1
Adverse event severity	Adverse event management	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013	5
Adverse event reversibility	Adverse event management	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013	5

Appendix Table 2 - 5: All process attributes extracted from all 25 DCE studies

Process Attribute	Final Categorization	Author	Study Count
Delivery method	Delivery method	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013; Kromer et al., 2015; Schaarschmidt et al., 2015; Eliasson et al., 2017; Guevara et al., 2017; Schaarschmidt et al., 2018	10
Injection type	Delivery method	Bolt et al., 2018	1
Duration	Duration	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013; Kromer et al., 2015; Schaarschmidt et al., 2015	7
Frequency	Frequency	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013; Kromer et al., 2015; Schaarschmidt et al., 2015; Guevara et al., 2017; Schaarschmidt et al., 2018; Feldman et al., 2019	10
Injection Regimen (frequency)	Frequency	Fairchild et al., 2017; Bolt et al., 2018	2
Treatment location	Location	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013; Kromer et al., 2015; Schaarschmidt et al., 2015; Guevara et al., 2017; Schaarschmidt et al., 2018	9
Who provides injection?	Location	Bolt et al., 2018	1
Laboratory tests	Other	Schaarschmidt et al., 2018	1
Injection discomfort or pain (if type of treatment included injections)	Other	Hauber et al., 2011	1
Type of treatment (frequency + location)	Process combination	Hauber et al., 2011; Tada et al., 2019	2

Appendix Table 2 - 5: All process attributes extracted from all 25 DCE studies

Process Attribute	Final Categorization	Author	Study Count
Route and frequency of therapy administration	Process combination	Torbica et al., 2014; Rigopoulos et al., 2018	2
Dosing (route of administration [ROA], setting, and frequency).	Process combination	Alcusky et al., 2017	1

Appendix Table 2 - 6: All cost-related attributes extracted from all 25 DCE studies

Cost Attribute	Final Categorization	Author	Study Count
Personal monthly out-of-pocket cost of treatment.	Cost to Patient	Hauber et al., 2011; Rigopoulos et al., 2018	2
Cost for the individual	Cost to Patient	Schaarschmidt et al., 2011; Schmieder et al., 2012; Umar et al., 2012; Schaarschmidt et al., 2013; Umar et al., 2013; Guevara et al., 2017; Schaarschmidt et al., 2018; Xu et al., 2018; Tada et al., 2019	9
Monthly treatment cost not covered by the National Health Service (NHS)	Cost to Patient	Torbica et al., 2014	1

3

Early health economic modelling for a treatment candidate in hidradenitis suppurativa

Chapter 3 was informed by:
Willems, D., Charokopou, M., Evers, S. M., & Hiligsmann, M. (2020). Early health economic modelling for a treatment candidate in hidradenitis suppurativa. *Journal of Medical Economics*, 23(12), 1516-1524.

3.1. Abstract

Aims: Hidradenitis suppurativa (HS) is a chronic skin condition causing inflammatory lesions, pain, scarring, impaired mobility, stigmatization, and malodor. Available treatment options are limited and often lack success implying the need for additional and improved treatment options. This research aims to estimate the potential economic value of a treatment candidate, to explore drivers of cost-effectiveness and to highlight economic evidence requirements for successful future value assessments.

Materials and methods: An early cost-effectiveness model was developed to assess the cost-effectiveness (expressed as cost per quality-adjusted life year (QALY) gained) of a treatment candidate compared against the only authorized biological treatment, adalimumab, for treating patients with moderate to severe HS from a UK National Health Service (NHS) and Personal Social Service (PSS) perspective. A targeted literature review on clinical and economic references and previous Health Technology Assessments (HTA) was performed for the development and validation of the early economic model used to present various sensitivity analyses accompanying the base-case cost-effectiveness results.

Results and limitations: The base-case results revealed the candidate not to be cost-effective compared to adalimumab when considering a formal cost-effectiveness threshold of £30,000 per QALY gained. Scenario- and threshold analyses highlighted that reducing dosing or drug price by half improves the cost-effectiveness of the candidate. The cost-effectiveness was highly sensitive to health states' utility values, treatment discontinuation and resource utilization, in line with existing HTA evidence. The paucity of economic studies and uncertainties around the candidate present methodological constraints that were addressed by presenting various sensitivity analyses.

Conclusions: Key costs- and health effects drivers were highlighted to contextualize under which circumstances a treatment candidate for the treatment of moderate to severe HS would reach acceptable cost-effectiveness levels. This early economic evaluation suggests promising economic perspectives for treatment candidates in HS. Exploring novel ways to use clinical endpoints to simulate the patient pathway and clinically meaningful treatment achievements in future research will facilitate the value demonstration of a candidate in a disease area where the unmet care need is high.

3.2. Introduction

Hidradenitis suppurativa (HS), also called acne inversa, is a common and chronic skin condition, most frequently occurring in patients after puberty until the early fifth decade of life(1). The prevalence rates vary in cohort studies between 0.7% and 4% but are mostly determined at below 1%(2). Underreporting, misreporting or maltreatment of HS by specialists is a frequently occurring problem as over 40% of patients only receive a correct HS diagnosis after more than 5 years of disease onset(2). The average duration of the disease was reported to be 18.8 years in a cohort at mean age 40(3). HS causes inflammation of the hair follicles, leading to boils, abscesses and scarring in armpits, genitals, groin, buttocks and perianal region (apocrine gland-bearing regions). Balieva et al. concluded that pain, impaired mobility, stigmatization, malodor and intimacy issues due to this skin condition severely affect patients' social lives, daily work and interpersonal relationships(4). Treatment options for HS are diverse, dependent on disease severity and often lack success(5). Whilst for the mild disease stage, antibiotics, antiseptics and simple surgical interventions can relieve acute symptoms, patients with moderate to severe HS often lack successful treatment options(6). The treatment of moderate to severe HS patients with first line options including antibiotics or antiseptics is recommended to be followed up with advanced procedures like the injection of biological therapies like adalimumab (ADA) or infliximab (IFX) and excisional surgery in case of lacking long-term treatment effect(7). In an Australian study, more than half of diagnosed patients were not receiving any treatment for their condition(8). ADA is currently the only approved biological treatment in Europe for HS and is recommended as option for treating moderate to severe HS patients in the UK, the reference country of this research(7,9). The limited number of successful treatment options causes a high humanistic disease burden in patients living with HS. Improved treatment management, possibly through newer and more efficacious treatment interventions is needed by patients and treating professionals(5). The economic burden of HS is high, with direct medical costs due to surgery being estimated at £2,027 per patient per year in the UK(10). Medical costs are observed to be up to 2.4 times higher for more severe HS patients(11). Indirect costs associated with frequent and long-term absenteeism and disability costs of HS patients further add to the socioeconomic burden of HS(12). HS appears to be a disease with low awareness and simultaneously seems to be a disease in which it is difficult to demonstrate treatment success due to the multifactorial pathogenesis of the disease(5). In the case of a promising treatment innovation being developed, the innovation must obtain marketing authorization by being of appropriate pharmaceutical quality, meeting effectiveness targets of the indication and showing safety in relation

to their efficacy(13). Subsequently before patients can access the innovative therapy, decision-makers and payers in national settings have to grant positive reimbursement recommendations, in many countries by performing a Health Technology Assessment (HTA). Economic evaluations are important elements of HTAs and require the innovation to demonstrate cost-effectiveness; the health benefits generated by the new intervention must be greater than those of the current standard of care at a cost level that remains within the willingness-to-pay (WTP) boundaries of payers(14). An emerging trend to increase the success rate of interventions in development is the use of early-stage cost-effectiveness modelling(15). This approach has become important to generate information for decision-making on the viability of new technologies and informs the generation of appropriate and timely evidence to maximize the likelihood for a positive HTA outcome(15,16). Such early economic evaluations facilitate the prediction of pricing and reimbursement scenarios for a technology in development(15). This research aims to critically appraise existing economic evaluations in HS with the objective to develop an early economic evaluation to assess the potential cost-effectiveness of a treatment candidate (CAND) in development. This economic evaluation adds value to existing evidence by estimating the possible economic value of a potential future treatment, exploring key drivers of cost-effectiveness and determining evidence elements and price levels that any future intervention is expected to meet in order to demonstrate economic value to decision authorities to achieve a positive reimbursement decision. This research is centered around the following research questions: i) what are the requirements in terms of costs and effects CAND for the treatment of moderate to severe HS must meet to achieve recommendation for reimbursement in the UK as reference country? ii) What are the predictors and most impactful drivers of cost-effectiveness for HS treatments in this study and how do these compare to drivers of previously published economic models?

3.3. Methods

This research consists of an early economic evaluation to compare long-term cost and health consequences of CAND to ADA for the treatment of moderate to severe HS. A targeted literature review (TLR) on existing clinical and economic evidence was first performed to have sufficient information to decide on clinical- and cost-considerations along with economic modelling techniques for the right target population.

3.3.1. Targeted literature review

The TLR in Medline was conducted using both controlled vocabulary, such as the National Library of Medicine's Medical Subject Headings (MeSH), and keywords. The TLR was performed to gain insights in four areas of interest: (i) data of clinical trials of treatments for HS, (ii) healthcare resource utilization, (iii) health-related quality of life studies and health care related utility data, iv) existing economic evaluations. In addition, HTA publications were searched with the purpose of investigating endpoints, methodologies and modeling techniques applied to economic evaluations of HS treatments and how those are perceived by the following HTA bodies:

- National Institute of Clinical Excellence (NICE) of England & Wales
- Pharmaceutical Benefits Advisory Committee (PBAC) of Australia
- Canadian Agency for Drugs and Technologies in Health (CADTH).

All searches were performed by one researcher (DW) and quality-checked by MH and MC, up to September 13th, 2019 and were limited to publications in English language. The search strategy is presented in the Appendix; all titles were selectively screened and reviewed per PICOS criteria in the Appendix.

3.3.2. Early economic modelling

The necessary steps to create the structure of a decision analytical model are described by Briggs, Claxton & Sculphner(17) and were followed in the development of the economic model. Microsoft Excel 2016 was used to develop the economic model. A Markov model was the modelling approach of choice because of its ability to represent multiple health states in a simple and straight-forward manner that reflects the disease progression and is consistent with the existing and validated economic model of ADA in the UK(18). The currently published economic model of ADA and its documentation in the technology appraisal (TA) 392 was frequently used as reference for model settings and data source for this research(18,19).

3.3.3. Model structure

The structure of the developed Markov model is depicted in Figure 3-1. It consists of five mutually exclusive model health states; due to data censoring around two health states (i.e., partial and high response) in TA392, it was only possible to populate three of five health states in the economic model of this research(18,19). In order to determine the response level of a patient, the validated Hidradenitis Suppurativa Clinical Response (HiSCR) 50 endpoint was used. All patients start the first model cycle in the non-responder health state; patients can die at any time

and will remain in this absorbing health state without occurring any costs or quality of life. The HiSCR50 endpoint measures the percentage of reduction of abscesses and inflammatory nodule count; a subject is considered a responder whenever a 50% or greater reduction of abscess and inflammatory nodule (AN) count without an increase in abscesses and draining fistula count is observed. The choice of this endpoint is in line with its clinical validation and consistent with the primary endpoint of ADA pivotal clinical trials(20,21). Variations of the HiSCR50 endpoint towards different cut off values were introduced in the economic model developed for ADA in TA392(18,19). NICE used a modified version of the HiSCR endpoint, stipulating that a 25% reduction in HiSCR is clinically meaningful to continue therapy with ADA(22). The modifications included a partial response (HiSCR25) and high response (HiSCR75) model health state to which a patient was assigned whenever a 25%-49% or 75-100% reduction of AN count, without an increase in abscesses and draining fistula count, was achieved respectively; however, any efficacy data on HiSCR25 and HiSCR75 endpoints was censored in TA382(18,19), hindering an accurate replication in this research and therefore highlighted grey in Figure 3-1. A lifetime time horizon was applied due to the chronic nature and relevance of the disease and is consistent with TA392(18,19).

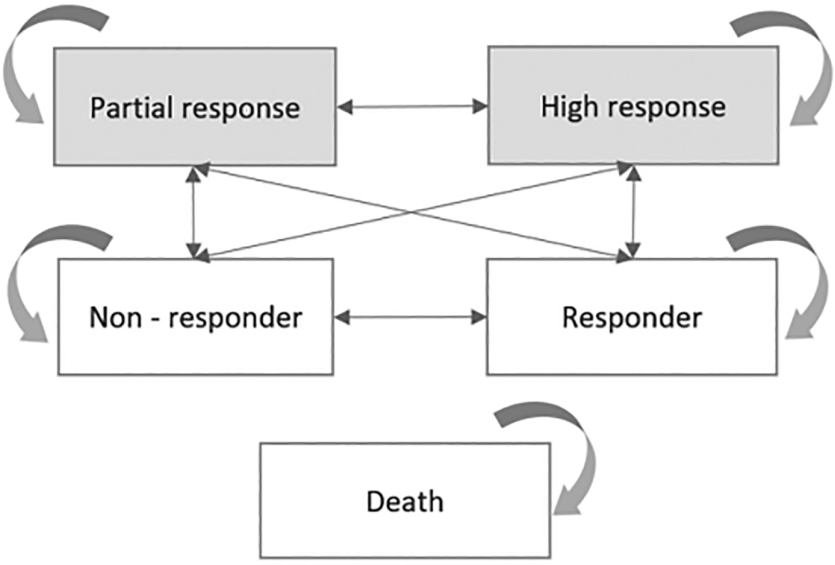


Figure 3 - 1: Model structure diagram.
Note: Model with 3 health states (white), 2 health states (grey) could not be replicated due to data censoring in TA392(18,19).

3.3.4. Target population

The population of interest for this research were adult patients (18 years or older) with moderate to severe HS which are not showing an adequate response to conventional therapies. These treatments usually include a combination of antibiotic therapy or surgical procedures(8). Patient age was set to 36 years in the base case, according to ADA pivotal trials and TA392(18,19,21)

3.3.5. Treatment interventions

ADA is a fully human monoclonal antibody against tumor necrosis factor-alpha, administered through bi-weekly subcutaneous injections (after load dose of 160 mg during first administration and 80 mg two weeks later)(5). ADA can be considered standard of care for this population because it is the only approved treatment for moderate to severe HS patients(5). CAND is a hypothetical biological treatment candidate for which efficacy, optimal dosing strategy and price are yet to be determined and therefore varied in the presented sensitivity analyses. ADA and CAND were both modelled as separate treatment strategies to assess the factors that impact the cost-effectiveness of CAND versus ADA. All patients receive treatment until week 12 and thereafter can discontinue treatment if response, defined by HiSCR50, is not achieved. Surgery was included in the model as health care resource and not as a separate treatment strategy to be consistent with TA392(18,19).

3.3.6. Clinical data and transition probabilities

The transitions between model health states were informed by ADA pooled efficacy data from the PIONEER I&II trials(21) until week 36 as depicted in Table 3-1 and their Open Label Extension (OLE) trial until week 252(23). The clinical performance of CAND in the absence of clinical data was based on assumptions. For the base case analysis, the CAND was assumed to show 30% higher response rates relative to ADA as a newer treatment would be expected to result in greater treatment response. The uncertainty around the magnitude of improved treatment was addressed by conducting multiple scenario analyses with varying the relative efficacy of CAND over ADA to 15% and 45%. Discontinuation rates from the OLE study for ADA(23) were applied beyond week 252 and fixed at 0.006 per 4-week. CAND was assumed to have 10% less discontinuation than ADA as the elevated treatment response levels are known to cause improved adherence in dermatologic diseases(24).

Table 3 - 1: Transition probabilities

Intervention	Adalimumab			Candidate		
Week	**Responder**	**Non-responder**	**Death**	**Responder**	**Non-responder**	**Death**
0	0.0%	100.0%	0.0%	0.0%	100.0%	0.0%
2	34.5%	65.5%	0.0%	44.8%	55.2%	0.0%
4	40.8%	59.2%	0.0%	53.0%	47.0%	0.0%
8	48.1%	51.9%	0.0%	62.5%	37.5%	0.0%
12	50.6%	49.4%	0.0%	65.8%	34.2%	0.0%
16	47.6%	52.3%	0.0%	61.9%	38.0%	0.0%
20	51.0%	49.0%	0.0%	66.3%	33.7%	0.0%
24	43.4%	56.6%	0.0%	56.4%	43.6%	0.0%
28	45.4%	54.6%	0.0%	59.0%	40.9%	0.0%
32	45.0%	54.9%	0.0%	58.5%	41.4%	0.0%
36	43.4%	56.5%	0.0%	56.4%	43.5%	0.0%

Note: For base case, candidate was assumed to have 30% relative higher response rates to adalimumab in its pivotal trials(21).

3.3.7. Costs and healthcare resource use data

In line with NICE guidelines(25), the perspective of the economic evaluation considers all costs relevant to NHS and PSS in the UK. Next to the treatment acquisition costs, healthcare services such as inpatient stays, outpatient visits, visits to wound-care (each for surgery-related and non-surgery related) and emergency department visits were accounted for in the economic evaluation. The healthcare utilization patterns of HS patients were derived from TA392(18,19), used independently of the treatment, but assigned to either response or non-response patients, presented in Table 3-2. All costs were inflated to 2019 values using Personal Social Services Research Unit (PSSRU) inflation indices(26).

Table 3 - 2: Costs and health care resource use

Treatment acquisition cost					
Treatment				**Adalimumab**	**Candidate**
Cost (£)/year				16,293	21,060
Dose				160mg w0,80 mg w2, 40 mg weekly	-
Source				(19)	+30% to ADA
Healthcare resource utilization					
Type of resource	**Unit cost (£)**	**Source**	**Unit of measure**	**Responders**	**Non-responders**
Accident & Emergency visits costs	132	(19)	Occurrence per patient/ year	0.16	0.52
Surgery-related costs					
Hospitalization	5,831	(19)	Occurrence per patient/ year	0.18	0.67
Outpatient visit	104	(19)	Occurrence per patient/ year	0.29	0.805
Visits to wound-care	104	(19)	Occurrence per patient/ year	0.15	0.625
Not surgery-related costs					
Hospitalization	2,339	(19)	Occurrence per patient/ year	0.17	0.37
Outpatient visit	104	(19)	Occurrence per patient/ year	3.31	4.56
Visits to wound-care	104	(19)	Occurrence per patient/ year	0.57	0.545
Adverse events					
Type of adverse event	**Unit cost (£)***	**Source****	**Unit of measure**	**Adalimumab**	**Candidate**
Headache	20	TA392	Occurrence per patient/4-week cycle	3.7%	3.7%

Table 3 - 2: Costs and health care resource use

Treatment acquisition cost					
Nasopharyngitis	13	TA392	Occurrence per patient/4-week cycle	1.9%	1.9%
Upper respiratory tract infection	147	TA392	Occurrence per patient/4-week cycle	1.4%	1.4%
Diarrhea	46	TA392	Occurrence per patient/4-week cycle	1.3%	1.3%
Gastroenteritis	125	TA392	Occurrence per patient/4-week cycle	0.5%	0.5%
Influenza	43	TA392	Occurrence per patient/4-week cycle	0.5%	0.5%
Bronchitis	147	TA392	Occurrence per patient/4-week cycle	0.2%	0.2%

*Note: Costs inflated to 2019 using PSSRU inflation indices and averaged between high response and response and partial response and no response. *The cost of each type of adverse event was estimated based on the assumed resource use required for the treatment of the adverse event. **Adverse events assumed similar for both treatment strategies.*

3.3.8. Health-related quality of life data (utilities)

Health-related quality of life (utility) data for the economic model were derived from the phase 3 PIONEER II trial data presented in TA392(18,21). The PIONEER II trial assessed the quality of life using EuroQoL-5-dimension (EQ-5D) data of all participants for up to 36 weeks. The utility values presented in TA392 across 5 model health states were averaged to 0.750, 0.529 and 0 for responders, non-responders and death, respectively, to fit the 3-health state model of this study.

3.3.9. Result presentation and uncertainty analyses

The analyses performed using the developed economic model were focused around exploring impactful value drivers, key data uncertainties and assumptions required. The cost-effectiveness results are presented as additional costs per QALY gained expressed by the incremental cost-effectiveness ratio (ICER), as recommended by NICE(25). By performing extensive deterministic sensitivity analyses in addition to distinct scenario analyses on dosing, prices and efficacy, the impact of model settings and parameters on cost-effectiveness results was assessed. Following the

presentation of base case results, the scenario analyses are presented as matrix for two price levels of CAND, varying relative efficacy of the CAND to ADA from 30% to 15% and 45%, while simultaneously changing dose of CAND from bi-weekly (Q2W) to weekly (QW) and four-weekly (Q4W). Multiple deterministic sensitivity analyses are presented in a tornado diagram to highlight parameters' impact on costs, health benefits and ICER separately(26). Lastly, a threshold analysis of the economically justifiable price for CAND is presented with the intent to estimate the maximum costs or minimum benefits that CAND must meet facing the comparator by applying the UK WTP threshold of £30k per QALY gained(27). Higher thresholds of £50k and £100k were additionally tested. The number of sensitivity analyses are aimed to address the uncertainties around the model structure- and input parameters; contrasting the findings with the TLR and HTA review findings is expected to increase external validation of the economic analyses.

3.4. Results

3.4.1. Targeted literature review

The TLR on clinical trials per search syntax (Appendix) revealed 89 sources, while identifying 123 studies reporting healthcare resource utilization for HS patients. Health-related quality of life and utility data of patients living with HS were revealed to be published in 241 titles and 25 references included information on economic evaluations of treatments used for HS. Three clinical trials of ADA served as key input source for clinical data evidence of the cost-effectiveness model of this research(21,23). The economic model presented for TA392 was assessed to be of sufficient quality to guide decision-making and serve as source of utility values and healthcare resource utilization for the development of the cost-effectiveness model of this research as it has led to the reimbursement of ADA for moderate to severe HS in UK(18,19). Reviewing HTA databases revealed five published health economics submissions of ADA for the treatment of moderate to severe HS of which a summary is presented in Table 3-3.

Table 3 - 3: Summary of HTA review

HTA body (country)	Date/ Source	Model structure	Clinical evidence source	Key outcomes	Decision	Key criticism
PBAC (Australia)	March 2016/ (29)	5 health state Markov model based on HiSCR	(20,21,23,28)	HiSCR	Rejected	Time horizon too long; re-initiation of ADA underestimated; HiSCR not measuring HRQoL, long-term discontinuation underestimated
PBAC (Australia)	July 2016/ (30)	5 health state Markov model based on HiSCR	(20,21,23,28)	HiSCR	Rejected	Long-term discontinuation underestimated; re -attempt treatment after failure
PBAC (Australia)	November 2016/ (31)	7 health state Markov model based on Hurley stage improvement	(20,21,23,28)	Hurley stage improve- ment, DLQI	Recommended under Risk Sharing agreement (agreement removed in 2018)	Disease progression not adequately modelled; no utility gain for responders; exaggerated higher costs for non-responders compared to responders
CADTH (Canada)	May 2016/ (32)	5 health state Markov model based on HiSCR	(20,21,23,28)	DLQI, HSQoL, SF-36, Health care resource utilization, other efficacy outcomes	Recommended (Conditions)	Residual effect of ADA overestimated; resource use calculation method; discontinuation unrealistically applied (12w vs 4w); stopping rule ADA not in line with expected clinical practice; model structure and transition probabilities neglecting varying baseline risk in clinical trials when applying the same response rate for all modelled patients.

Table 3 - 3: Continued.

HTA body (country)	Date/ Source	Model structure	Clinical evidence source	Key outcomes	Decision	Key criticism
NICE (England)	June 2016/ (18,19,33)	5 health state Markov model based on HiSCR	(20,21,23,28)	Primary: HiSCR, Secondary and others HRQoL	Recommended under Patient Access Scheme	IFX not as comparator option; questionable source of resource utilization; missing clinical validation of HiSCR25 and HiSCR75; doubts if threshold used for stopping rule (HiSCR25) is clinically meaningful; overestimation of surgery need; questionable appropriateness of pooling PIONEER I&II data; use of unblinded OLE study for week 36 onwards; method of applying discontinuation rates; technical model errors

Note: HiSCR: Hidradenitis Suppurativa Clinical Response, ADA: adalimumab, HRQoL: health-related quality of life, DLQI: Dermatology Life Quality Index, HSQoL: Hidradenitis Suppurativa Quality of Life, SF-36:Short Form (36) Health Survey, IFX: Infliximab, OLE study: Open label extension study.

3.4.2. Results of economic analyses

3.4.2.1. Base case analysis

For the base case analysis, CAND was assumed to have 30 % higher response rates relative to ADA and 30% annual price premium relative to ADA, which yielded an ICER when comparing CAND to ADA of £132,952 per QALY gained. The ICER indicates that CAND is not cost-effective at a formal WTP threshold of £30k/QALY gained as applied in the UK (Table 3-4).

Table 3 - 4: Base case results

Therapy	Therapy costs	Resource use costs	AE costs	Total costs	Total QALYs	In-cremen-tal costs	In-cremen-tal QALYs	ICER (£/ QALY)
Adalimumab	£103,321	£105,672	£471	£209,465	13.596	-	-	-
Candidate	£174,560	£97,817	£615	£272,993	14.073	£63,528	0.48	£132,952

Note: All health effects and costs discounted at 3.5% per annum.
AE: adverse events, QALY: quality-adjusted life year, ICER: Incremental cost-effectiveness ratio.

3.4.2.2. Scenario analysis

Results of the scenario analyses assessing the impact of uncertainty regarding price, dosing and efficacy on the cost-effectiveness of CAND are presented in Table 3-5.

Table 3 - 5: Scenario analyses results

10% price premium to ADA**		**Dose of CAND**		
		QW	Q2W	Q4W
	15%	£581,448	£93,185	dominant
Efficacy relative to ADA	30%	£381,724	£76,749	dominant
	45%	£304,114	£70,362	dominant
30% price premium to ADA**		**Dose of CAND**		
		QW	Q2W	Q4W
	15%	£760,345	£183,306	dominant
Efficacy relative to ADA	30%	£493,378	£132,953*	dominant
	45%	£389,638	£113,386	dominant
50% price premium to ADA**		**Dose of CAND**		
		QW	Q2W	Q4W
	15%	£939,241	£273,428	dominant
Efficacy relative to ADA	30%	£605,031	£189,156	dominant
	45%	£475,162	£156,409	dominant

*Note: *Base case analysis. Results presented as costs (£) per additional QALY gained. **relative annual treatment acquisition costs of CAND to ADA. Efficacy percentage represents the relative treatment efficacy to ADA efficacy derived from Kimball et al. (21).*
ADA: adalimumab, CAND: candidate, QW: every week, Q2W: every other week, Q4W: four-weekly.

All three parameters i.e., price, dosing and relative efficacy impacted the ICERs of CAND against ADA. In all scenarios in which the dosing of CAND is reduced to Q4W, irrespective of relative efficacy tested, CAND was demonstrated to dominate ADA (greater QALYs at lower costs).

3.4.2.3. Deterministic Sensitivity analyses

Figure 3-2 depicts the analyses assessing the effect of diverse parameters on the ICER of CAND against ADA (base case £132,953/QALY gained). The results of the sensitivity analyses on costs and health effects separately are presented in the Appendix and suggest that discount rates have greatest impact on health effects and costs. Across all deterministic sensitivity analyses, the cost-effectiveness of CAND against ADA was demonstrated to be most sensitive to the utility values, time horizon, discontinuation rates and resource utilization patterns.

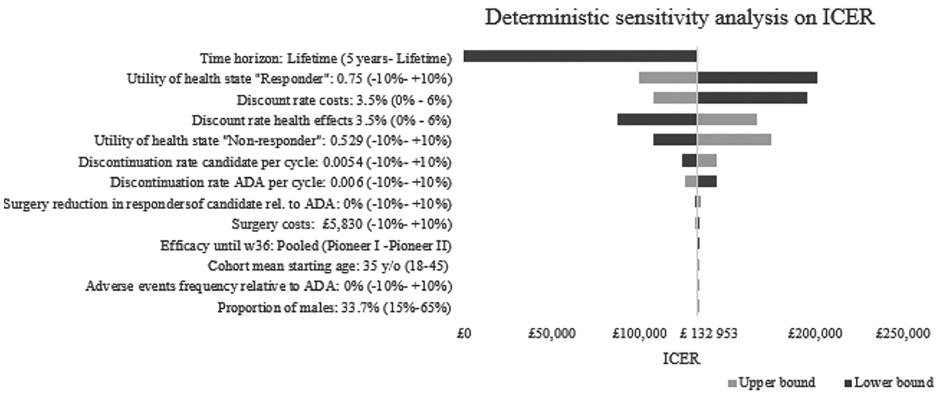


Figure 3 - 2: Deterministic sensitivity analyses.
Note: ICER: Incremental cost-effectiveness ratio, ADA: adalimumab.

3.4.2.4. Threshold analyses: Economically justifiable price

Threshold analyses to determine the required relative price difference and relative efficacy level between CAND and ADA in order to meet different WTP thresholds are presented in Figure 3-3.

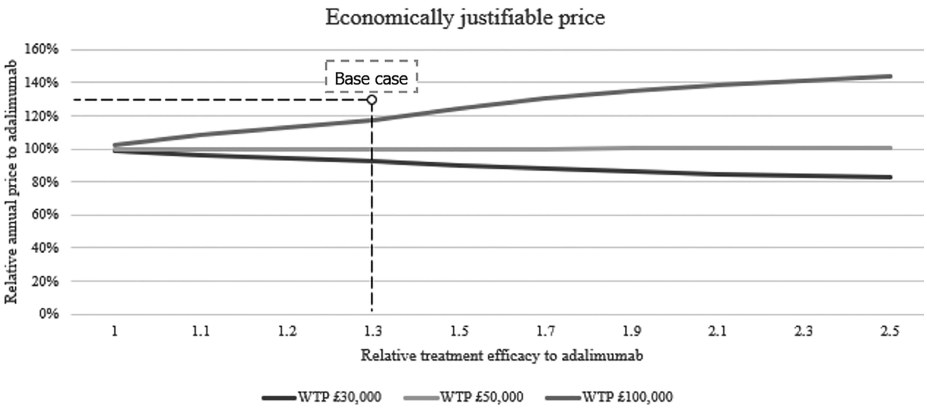


Figure 3 - 3: Threshold analyses: Economically justifiable price.
Note: 1=CAND equal efficacy to ADA, 100% indicate price parity of CAND to ADA; WTP: willingness-to-pay.

3.4.3. Model validation

The developed model is expected to embody a high degree of face validity due to the elaborate targeted literature review, whose findings served as decision criteria and input data. Additionally, face validity was further assured by clearly identifying, describing and justifying data sources, assumptions and decisions that had to be made in the modelling process. However, cross-validation, the comparison of a model with a similar model, remains difficult because many inputs of the ADA model in TA392 remain censored(18,19). Further research and increased transparency in health economic modelling practices in HS is required to bridge the exposed data gap and to allow broader types of model validations when developing future economic models to assess the cost-effectiveness of treatments for HS.

3.5. Discussion

Given the nature of this research being an early economic evaluation to assess the potential economic value of treatment candidate without mature clinical evidence on efficacy and dosing, it was expected to underly a degree of uncertainty with regards to the characteristics of CAND for which only hypothetical parameters were chosen relative to its comparator ADA. With base case settings, CAND was demonstrated to not achieve acceptable cost-effectiveness levels when applying a £30k WTP threshold. As various sensitivity analyses have revealed, numerous parameters markedly affected the cost-effectiveness of CAND against ADA. Discontinuation rates, time horizon, treatment acquisition costs, dosing and efficacy were observed to have greatest impact on the ICER. While further clinical development of any candidate reduces treatment-specific parameter uncertainty, patient- and clinical expert opinion must be considered to address uncertainties on structural model parameters and assumptions for future economic analyses. The provided scenario analyses have revealed promising findings for future development of investigational therapies in HS. Optimized long-term dosing, maintenance data of high efficacy and reduced discontinuation may ease value demonstration of future treatment candidates against the standard of care for moderate to severe HS. Probabilistic scenario analyses (PSA) were not conducted due to unknown uncertainty levels of CAND hypothetical input parameters; scenario-, sensitivity- and threshold analyses were conducted to address this limitation. The economically justifiable price analyses to determine the relative price- and efficacy levels of CAND over ADA in order for CAND to meet a pre-defined WTP threshold revealed a negative relationship between increasing price and efficacy for the lowest WTP threshold of £30k per QALY gained; this finding can be considered controversial as it indicates that CAND can be offered at a higher price if the relative efficacy

to ADA is lower. This counterintuitive finding may be attributable to the missing treatment stopping rule as used for ADA in TA392. Such stopping rules aim to optimize treatment usage only for recipients for which meaningful treatment results are achieved and hence can improve the cost-effectiveness of interventions. In TA392(18,19), the stopping rule suggests that patients who do not achieve a HiSCR25 discontinue treatment, however, it was not possible to replicate this stopping rule due to data on HiSCR25 being censored in TA392(18,19). Data censoring of such sort in HTA documentations economic models can limit following economic evaluation aiming to demonstrate cost-effectiveness of novel therapies. For this research in HS, censoring of clinical and economic evidence in TA392 of ADA of HiSCR25 and HiSCR75 health states has prevented a more accurate replication of ADA economic model because these two health states could not be populated. The 5-health statement model used in TA392(18,19) had to be scrutinized to a binary response type by using a 3-health state model. This discrepancy of model structure (3 vs. 5 health state model) is considered to have contributed to differing proportions of responders and their associated cumulative costs and QALYs when compared to TA392(18,19). Although the stopping rule and number of health states differ, many other settings and input data are consistent with a previous application of ADA(18,19). In all published economic evaluations of HS treatments reviewed for this study, treatment continuation rates and long-term benefits were consistently appraised to be an important driver of cost-effectiveness which underlines the importance to generate high quality evidence on maintenance of efficacy and treatment continuation. An early economic evaluation as conducted for this study is useful to estimate the value demonstration potential of a treatment candidate and can reveal evidence generation opportunities to improve the outcomes of future reimbursement decision-making. Reducing the long-term dosing scheme while maintaining a high therapeutic response could improve the economic value demonstration potential of a future HS therapy. This research has exposed a critical limitation of adapting pre-existing models for HS without having access to the full underlying datasets, future research should focus on generating clinical efficacy-, quality of life- and economic data across a broader range of HiSCR levels than only HiSCR50 e.g., HiSCR75, HiSCR90 or HiSCR100. Furthermore, improved data on long-term treatment response and treatment compliance are important to generate as these were demonstrated to be most influential on cost-effectiveness results. The revealed challenges due to important HTA evidence being censored for the standard of care (ADA) will persist for future economic evaluations aiming to demonstrate worthiness to invest more money for greater long-term treatment benefits achieved with a new therapy for moderate to severe HS patients.

3.6. Conclusions

Early economic modelling research provides the opportunity to explore the potential economic value of an investigational therapy for many stakeholders involved in the process of developing and making treatment interventions available to patients and professionals. While CAND was not demonstrated to be cost-effective in the base case analysis, key cost- and health effect drivers were highlighted in various sensitivity analyses to contextualize under which grounds a future candidate can be cost-effective. Further evidence generation will enable suitable differentiation strategies, increasing the chances of a therapy in development to be accepted by payers in the HTA process, which is required before patients with HS can access such interventions.

3.7. References

1. Dufour, D., Emtestam, L., & Jemec, G. (2014). Hidradenitis suppurativa: a common and burdensome, yet under-recognised, inflammatory skin disease. *Postgraduate medical journal*, 90(1062), 216-221.
2. Sabat, R., Jemec, G. B., Matusiak, Ł., Kimball, A. B., Prens, E., & Wolk, K. (2020). Hidradenitis suppurativa. *Nature Reviews Disease Primers*, *6*(1), 1-20.
3. Von der Werth, J., & Williams, H. (2000). The natural history of hidradenitis suppurativa. *Journal of the European Academy of Dermatology and Venereology*, 14(5), 389-392.
4. Balieva, F., Kupfer, J., Lien, L., Gieler, U., Finlay, A. Y., Tomás-Aragonés, L., ... & Halvorsen, J. A. (2017). The burden of common skin diseases assessed with the EQ-5D™: a European multicenter study in 13 countries. *British Journal of Dermatology*, 176(5), 1170-1178.
5. Matusiak, Ł., Jemec, G., & Szepietowski, J. (2019). Pharmacological development in hidradenitis suppurativa. *Current opinion in pharmacology*, 46, 65-72.
6. Rambhatla, P., Lim, H., & Hamzavi, I. (2012). A systematic review of treatments for hidradenitis suppurativa. *Archives of Dermatology*, 148(4), 439-446.
7. Zouboulis, C., Desai, N., Emtestam, L., Hunger, R., Ioannides, D., Juhász, I., ... & Schneider-Burrus, S. (2015). European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. *Journal of the European Academy of Dermatology and Venereology*, 29(4), 619-644.
8. Calao, M., Wilson, J., Spelman, L., Billot, L., Rubel, D., Watts, A. , & Jemec, G. (2018). Hidradenitis Suppurativa (HS) prevalence, demographics and management pathways in Australia: A population-based cross-sectional study. *PloS one*, *13*(7).
9. National Institute for Health and Care Excellence. (2016). *Adalimumab for treating moderate to severe hidradenitis suppurativa TA392*.
10. Desai, N., & Shah, P. (2017). High burden of hospital resource utilization in patients with hidradenitis suppurativa in England: a retrospective cohort study using hospital episode statistics. *British Journal of Dermatology*, 176(4), 1048-1055.
11. Kosunen, M. , Ranta, M., Hirvonen, M., Pasternack, R., & Sintonen, H. (2018). PSS22-Economic burden of disease of hidradenitis suppurativa in Finland: results from the HI-FI study. *Value in Health*, *21*, S426.
12. Tzellos, T., Yang, H., Mu, F., Calimlim, B., & Signorovitch, J. (2019). Impact of hidradenitis suppurativa on work loss, indirect costs and income. *British Journal of Dermatology*, *181*(1), 147-154.
13. Rawlins, M. D. (2012). Crossing the fourth hurdle. *British Journal of Clinical Pharmacology*, 73(6), 855-860.
14. Van Wilder, P., Mabilia, V., Kuipers Cavaco, Y., & McGuinn, J. (2015). Towards a Harmonised EU Assessment of the Added Therapeutic Value of Medicines. *Study of the ENVI Committee*. Retrieved on September 13th, 2019, from: http://www. europarl. europa.eu/RegData/etudes/STUD/2015/542219/IPOL_STU (2015) 542219_EN.pdf
15. IJzerman, M. J., Koffijberg, H., Fenwick, E., & Krahn, M. (2017). Emerging use of early health technology assessment in medical product development: a scoping review of the literature. *Pharmacoeconomics*, *35*(7), 727-740.

16. Tu, H., Han, D., Pechlivanoglou, P., Miller, F., Rac, V., Chin, W., Tricco, A., Paulden, M., Bielecki, J. & Krahn, M. (2014). Early economic evaluation of emerging health technologies: protocol of a systematic review. *Systematic Reviews*, 3(1), 81.
17. Briggs, A., Sculpher, M., & Claxton, K. (2006). *Decision modelling for health economic evaluation*. OUP Oxford.
18. National Institute for Clinical Excellence. (2016). Adalimumab for treating moderate to severe hidradenitis suppurativa (TA392). Retrieved on September 13th, 2019, from: https://www.nice.org.uk/guidance/ta392/chapter/4-Committee-discussion.
19. Tappenden, P., Carroll, C., Stevens, J., Rawdin, A., Grimm, S., Clowes, M. (2016). *Adalimumab for treating moderate to severe hidradenitis suppurativa: a single technology appraisal. Addendum: Patient access scheme.* University of Sheffield; Retrieved on September 13th, 2019, from: https://www.nice.org.uk/guidance/TA392/documents/committee-papers.
20. Kimball, A., Sobell, J., Zouboulis, C., Gu, Y., Williams, D., Sundaram, M., ... & Jemec, G. (2016a). HiSCR (Hidradenitis Suppurativa Clinical Response): a novel clinical endpoint to evaluate therapeutic outcomes in patients with hidradenitis suppurativa from the placebo-controlled portion of a phase 2 adalimumab study. *Journal of the European Academy of Dermatology and Venereology*, 30(6), 989-994.
21. Kimball, A., Okun, M., Williams, D., Gottlieb, A., Papp, K., Zouboulis, C., ... & Korman, N. (2016b). Two phase 3 trials of adalimumab for hidradenitis suppurativa. *New England Journal of Medicine*, 375(5), 422-434.
22. Ingram, J. , Collier, F., Brown, D., Burton, T., Burton, J., Chin, M., ... & Exton, L. (2019). British Association of Dermatologists guidelines for the management of hidradenitis suppurativa (acne inversa) 2018. *British Journal of Dermatology*, *180*(5), 1009-1017.
23. Zouboulis, C., Okun, M. , Prens, E., Gniadecki, R., Foley, P., Lynde, C., ... & Jemec, G. (2019). Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. *Journal of the American Academy of Dermatology*, 80(1), 60-69.
24. Feldman, S. R., Horn, E. J., Balkrishnan, R., Basra, M. K., Finlay, A. Y., McCoy, D., ... & Council, I. P. (2008). Psoriasis: improving adherence to topical therapy. Journal of the American Academy of Dermatology, 59(6), 1009-1016.
25. National Institute for Health and Care Excellence. (2013). *Guide to the methods of technology appraisal (PMG9).* Retrieved on September 13th, 2019, from: https://www.nice.org.uk/process/pmg9/chapter/introduction.
26. Curtis, L., & Bruns, A. (n.d.). *Unit Cost of Health & Social Care 2019.* Personal Social Services Research Unit, Kent Academic Repository. https://doi.org/10.22024/UniKent%2F01.02.79286
27. Claxton, K., Martin, S., Soares, M., Rice, N., Spackman, E., Hinde, S., ... & Sculpher, M. (2015). Methods for the estimation of the National Institute for Health and Care Excellence cost-effectiveness threshold. *Health technology assessment (Winchester, England)*, *19*(14), 1.
28. Kimball, A., Kerdel, F., Adams, D., Mrowietz, U., Gelfand, J., Gniadecki, R., ... & Rosenfeld, M. (2012). Adalimumab for the treatment of moderate to severe hidradenitis suppurativa: a parallel randomized trial. *Annals of internal medicine*, 157(12), 846-855.

29. Pharmaceutical Benefits Advisory Committee: *Adalimumab for the initial treatment of moderate-to-severe Hidradenitis Suppurativa (Public Summary document)*, March 2016. Retrieved on September 13th, 2019, from: http://www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-03/files/adalimumab-psd-march-2016.docx.
30. Pharmaceutical Benefits Advisory Committee: *Adalimumab for the initial treatment of moderate-to-severe Hidradenitis Suppurativa (Public Summary document)*, July 2016. Retrieved on September 13th, 2019, from: www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-07/files/adalimumab-psd-july-2016.docx.
31. Pharmaceutical Benefits Advisory Committee: *Adalimumab for initial treatment and Authority Required (Streamlined) listing for continuation of adalimumab for the treatment of moderate to severe hidradenitis suppurativa (HS) (Public Summary Document)*, November 2016. Retrieved on September 13th, 2019, from: www.pbs.gov.au/industry/listing/elements/pbac-meetings/psd/2016-11/files/adalimumab-psd-november-2016.docx.
32. Canadian Agency for Drugs and Technologies in Health: *Common Drug Review (CDR) Pharmacoeconomic review report for Humira*, May 2016. Retrieved on September 13th, 2019, from: https://cadth.ca/sites/default/files/cdr/pharmacoeconomic/SR0455_HumiraHS_PE_Report.pdf.
33. Tappenden, P., Carroll, C., Stevens, J., Rawdin, A., Grimm, S., Clowes, M., ... & Ghazavi, M. (2017). Adalimumab for Treating Moderate-to-Severe Hidradenitis Suppurativa: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. *PharmacoEconomics*, 35(8), 805-815.

3.8. Appendix

Appendix Table 3 - 1: Search syntax

Number	Search	Hits
1	Hidradenitis, suppurativa	2382
2	“2000/01/01”[PDAT] : “ 2019/09/13”[PDAT]	2043
3	English[lang]	1929
Clinical trials		
	((“hidradenitis suppurativa”[MeSH Terms] OR (“hidradenitis”[All Fields] AND “suppurativa”[All Fields]) OR “hidradenitis suppurativa”[All Fields] OR (“hidradenitis”[All Fields] AND “suppurativa”[All Fields])) AND (“2000/01/01”[PDAT] : “2019/09/13”[PDAT]) AND English[lang]) AND (((((“double-blind method”[MeSH Terms] OR (“double-blind”[All Fields] AND “method”[All Fields]) OR “double-blind method”[All Fields] OR (“double”[All Fields] AND “blind”[All Fields] AND “method”[All Fields]) OR “double blind method”[All Fields]) OR (“randomized controlled trial”[Publication Type] OR “randomized controlled trials as topic”[MeSH Terms] OR “randomized controlled trial”[All Fields] OR “randomised controlled trial”[All Fields])) OR (“random allocation”[MeSH Terms] OR (“random”[All Fields] AND “allocation”[All Fields]) OR “random allocation”[All Fields])) OR (“clinical trial”[Publication Type] OR “clinical trials as	89
Utilities		
4	((“hidradenitis suppurativa”[MeSH Terms] OR (“hidradenitis”[All Fields] AND “suppurativa”[All Fields]) OR “hidradenitis suppurativa”[All Fields] OR (“hidradenitis”[All Fields] AND “suppurativa”[All Fields])) AND (“2000/01/01”[PDAT] : “2019/09/13”[PDAT]) AND English[lang]) AND (Quality of life[tiab] OR Life quality[tiab] OR Hql[tiab] OR sf 36[tiab] OR sf36[tiab] OR ((“Sociol Forum (Randolph N J)”[Journal] OR “sf”[All Fields]) AND thirtysix[tiab]) OR ((“Sociol Forum (Randolph N J)”[Journal] OR “sf”[All Fields]) AND thirty six[tiab]) OR short form 36[tiab] OR (short[All Fields] AND form[All Fields] AND thirty six[tiab]) OR (short[All Fields] AND form[All Fields] AND thirty-six[tiab]) OR qol[tiab] OR euroqol[tiab] OR eq5d[All Fields] OR eq 5d[tiab] OR Qaly$[tiab] OR Quality adjusted life year$[tiab] OR Hye$[tiab] OR ((“health”[MeSH Terms] OR “health”[All Fields]) AND year$ equivalent$[tiab]) OR (health utilities[tiab] OR health utility[tiab]) OR hui[tiab] OR (Quality[All Fields] AND of wellbeing$[tiab]) OR (Quality[All Fields] AND of wellbeing[tiab]) OR qwb[tiab] OR qald$[tiab] OR qale$[tiab] OR qtime$[tiab] OR Standard gamble$[tiab] OR Time trade off[tiab] OR Time tradeoff[tiab] OR tto[tiab] OR Visual analog$ scale$[tiab] OR Discrete choice experiment$[tiab] OR sf6[tiab] OR sf 6[tiab] OR short form 6[tiab] OR (shortform[All Fields] AND 6[tiab]) OR sf six[tiab] OR (shortform[All Fields] AND six[tiab]) OR short form six[tiab] OR (health state utilities[tiab] OR health state utility[tiab]) OR Health state$ value$[tiab] OR health state$ preference$[tiab]) AND ((“2000/01/01”[PDAT] : “2019/09/13”[PDAT]) AND English[lang])	241

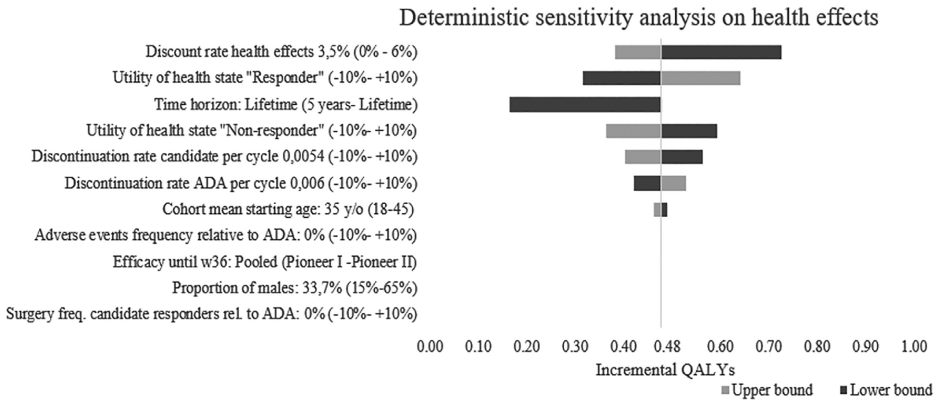
Healthcare resource use		
5	(((“hidradenitis suppurativa”[MeSH Terms] OR (“hidradenitis”[All Fields] AND “suppurativa”[All Fields]) OR “hidradenitis suppurativa”[All Fields] OR (“hidradenitis”[All Fields] AND “suppurativa”[All Fields])) AND (“2000/01/01”[PDAT] : “2019/09/13”[PDAT]) AND English[lang]) AND (“health resources”[MeSH Terms] OR “health care use”[tiab] OR “healthcare use”[tiab] OR “health service use”[tiab] OR “health services use”[tiab] OR “health care utilisation”[tiab] OR “healthcare utilisation”[tiab] OR “healthcare utilization”[tiab] OR “health care utilization”[tiab] OR “health resource utilization”[tiab] OR “health resource utilisation”[tiab] OR “health service utilisation”[tiab] OR “health service utilization”[tiab] OR “health services utilisation”[tiab] OR “health services utilization”[tiab] OR “resource use”[tiab] OR “length of stay”[MeSH Terms] OR (“length”[tiab] AND “stay”[tiab]) OR “length of stay”[tiab] OR (“hospital”[tiab] AND “stay”[tiab]) OR “hospital stay”[tiab] OR “Hospital visit”[tiab] OR “hospitalization”[MeSH Terms] OR Hospitalization[tiab] OR Hospitalisation[tiab] OR (productiv[tiab] OR productiva[tiab] OR productive[tiab] OR productive’[tiab] OR productiveand[tiab] OR productivee[tiab] OR productively[tiab] OR productiveness[tiab] OR productives[tiab] OR productividad[tiab] OR productivion[tiab] OR productivism[tiab] OR productivism’[tiab] OR productivist[tiab] OR productivist’[tiab] OR productivit[tiab] OR productivite[tiab] OR productivites[tiab] OR productivities[tiab] OR productivitiy[tiab] OR productivity[tiab] OR productivity’[tiab] OR productivity’s[tiab] OR productivityand[tiab] OR productivitycan[tiab] OR productivitydagger[tiab] OR productivityin[tiab] OR productivitymodeling[tiab] OR productivityof[tiab] OR productivitywhen[tiab] OR productivo[tiab] OR productivos[tiab] OR productivties[tiab]) OR absenteeism[tiab] OR “absenteeism”[MeSH Terms] OR “emergencies”[MeSH Terms] OR “emergencies”[tiab] OR “emergency”[tiab] OR “Home care”[tiab] OR “palliative care”[MeSH Terms] OR (“palliative”[tiab] AND “care”[tiab]) OR “palliative care”[tiab] OR “Out of pocket”[tiab] OR “Ambulatory visit”[tiab] OR “outpatients”[MeSH Terms] OR “outpatients”[tiab] OR “outpatient”[tiab] OR “inpatients”[MeSH Terms] OR “inpatients”[tiab] OR “inpatient”[tiab] OR Radiology[tiab] OR imaging[tiab] OR microcosting[tiab] OR “resource burden”[tiab] OR “caregivers”[MeSH] OR “caregiver*”[tiab] OR “sick leave”[MeSH] OR “sick leave”[tiab] OR “family leave”[MeSH] OR “family leave”[tiab] OR “parental leave”[MeSH] OR “parental leave”[tiab] OR “work days”[tiab] OR cost[tiab])) AND (“2000/01/01”[PDAT] : “2019/09/13”[PDAT]) AND English[lang]	123

Econonomic models		
	((“hidradenitis suppurativa”[MeSH Terms] OR (“hidradenitis”[All Fields] AND “suppurativa”[All Fields]) OR “hidradenitis suppurativa”[All Fields] OR (“hidradenitis”[All Fields] AND “suppurativa”[All Fields])) AND (“2000/01/01”[PDAT] : “2019/09/13”[PDAT]) AND English[lang]) AND (“Cost-Benefit Analysis”[Mesh] OR Cost[tiab] OR Resources[tiab] OR Economic evaluation[tiab] OR Economic model[tiab] OR Cost effectiveness[tiab] OR Cost utility[tiab] OR Cost minimization[tiab] OR Cost benefit[tiab]) AND ((“2000/01/01”[PDAT] : “2019/09/13”[PDAT]) AND English[lang])	25

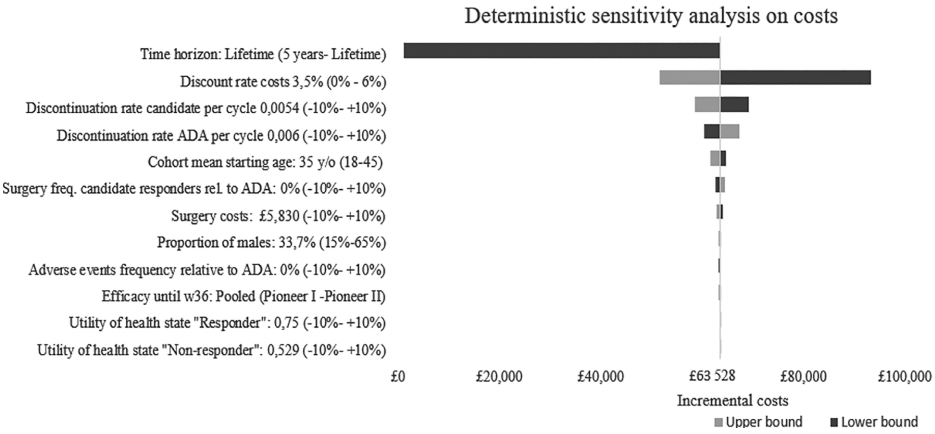
Appendix Table 3 - 2: PICOS selection criteria

Criteria	Inclusion criteria	Exclusion criteria
Population	• Male or female subjects over 18 years old • Subjects that have been diagnosed with Hidradenitis Suppurativa	• Patients younger than 18 years old • Patients not diagnosed with Hidradenitis Suppurativa
Intervention	Candidate OR Existing interventions aimed at managing HS such as: • Antibiotics • Surgery • Antiseptics • Adalimumab/Humira • Infliximab (off-label)	• Treatments other than those listed in the inclusion criteria • Treatment listed in the inclusion criteria but not used to treat HS.
Comparator	Treatment options • Antibiotics • Surgery • Antiseptics • Adalimumab/Humira • Infliximab (no market authorization) OR placebo	• Treatments other than those listed in the inclusion criteria • Treatment listed in the inclusion criteria but not used to treat HS.
Outcomes	Efficacy • Physician-reported outcomes (AN count, PGA, Sartorius score) • Patient-reported outcomes (QoL, DLQI, EQ-5D, pain scales) Safety • Adverse events Healthcare utilization • Resource use	• If outcomes of interest are not reported
Study Design	• Randomized control trials with double-blinded design – with active or placebo as comparator • Single arm trials – with no comparator • Open label clinical trials • Economic evaluation papers fully describing economic modelling methods e.g. cost-utility analysis, cost-effectiveness analysis will be included. • English language only	• Pharmacokinetic Studies • Editorials • Letters to the editor • Studies published in languages other than English • Observational studies

Note: HS: Hidradenitis Suppurativa, AN: absolute nodule, PGA: physician global assessment, QoL: quality of life, DLQI: dermatology life quality index, EQ-5D: EuroQOL-5 dimensions.



Appendix Figure 3 - 1: Deterministic sensitivity analyses on health effects expressed as QALYs.
Note: ADA: adalimumab, QALY: quality-adjusted life year, w36: week 36.



Appendix Figure 3 - 2: Deterministic sensitivity analysis on costs.
Note: ADA: adalimumab, w36: week 36.

4

Identifying unmet care needs and important treatment attributes in the management of hidradenitis suppurativa: a qualitative interview study

Chapter 4 was informed by: Willems, D., Hiligsmann, M., Van der Zee, H. H., Sayed, C. J., & Evers, S. M. (2021). Identifying unmet care needs and important treatment attributes in the management of hidradenitis suppurativa: a qualitative interview study. *The Patient – Patient-Centered Outcomes Research*, 1-12.

4.1. Abstract

Background: Hidradenitis suppurativa (HS) is an inflammatory skin disease with profound effect on patients' quality of life (QoL). The patient's journey to manage HS is often complex and unsuccessful which motivates the aim of this research to gain insight into unmet needs and relevant treatment considerations from the perspective of patients and health care professionals (HCPs).

Methods: Individual semi-structured interviews were conducted with patients and HCPs experienced in treating HS to understand the perceived unmet care needs and to identify important treatment attributes. Prioritization of the five most important treatment attributes allowed elicitation of their relative importance.

Results: Interviews with 12 patients and 16 HCPs revealed 16 areas of unmet needs either related to treatment outcomes or the care process and 13 important treatment attributes. The most frequently reported unmet needs by patients and HCPs were lacking QoL improvement, low treatment effectiveness, inadequate pain control, low disease awareness and delayed diagnosis. Patients expressed unique concerns relating to pain management, access to HS specialists and wound care guidance and costs, which HCPs did not. Treatment attributes related to effectiveness were considered most important by patients and HCPs. Patients additionally emphasized a strong preference for improved pain management.

Conclusions: Current HS treatments and care processes leave patients and HCPs with a high level of unmet need. It is critical to consider patients' and HCP's perspectives when designing appropriate HS care as perceived unmet needs differ. Further quantitative preference elicitation studies are needed to assess the trade-offs between important care needs and treatment attributes.

4.2. Introduction

Hidradenitis suppurativa (HS), also known as acne inversa is a chronic, debilitating inflammatory skin disease, with an overall prevalence ranging from 0.03% to 1% and average age of disease onset of 22 years(1). The disease involves chronic or recurring inflamed lesions with suppuration, which cause pain and scars in predominantly inverse body areas(2-5). Although HS itself causes substantial morbidity, recent evidence has shown that HS is a systemic inflammatory disease with multiple associated comorbidities that collectively decrease the quality of life of patients(6). Patients with HS frequently suffer from conditions like obesity and metabolic syndrome as well as psychologic problems such as depression, tobacco dependency, and social stigmatization which add to the disease burden(7-12). Such disease consequences have a substantial negative impact on general and skin-specific quality of life (QoL)(13,14). HS is frequently misdiagnosed with an average duration from manifestation of first symptoms until diagnosis reported of 10.0 ± 9.6 (mean ± SD) years despite existence of published diagnostic criteria(5,15-17). Due to the multifaceted nature of the disease, its course can be unpredictable which poses challenges for patients and health care professionals (HCPs) in the management of the disease(16). Guidelines suggest the use of antibacterial treatment for mild to moderate HS and anti-inflammatory treatments for more severe HS, with surgery recommended to manage sinus tracts, scars and anatomic changes that have manifested(3). The TNF-α inhibitor adalimumab is to date the only approved biologic therapy in EU and US. Despite treatment, only approximately one-third of patients experience remission of their disease over time with currently available treatment options and almost half of treated HS patients remain dissatisfied due to poor efficacy, undesirable adverse effects, inconvenience or invasiveness(2,16,18). Many patients therefore experience a disease that continues to progress over years, which implies that there is still significant unmet need for additional effective management options(18). Other biologics targeting TNF-α, interleukin (IL)-17, IL-23, and other cytokines have been reported in smaller studies and may potentially have efficacy for the treatment of HS(3,18-21). There is a potential influx of additional treatments with over 10 small molecule- or biological treatments in clinical development for HS, with only bimekizumab and secukinumab (both monoclonal antibodies against IL-17) currently being tested in phase 3 clinical trials(19,22). Studies exploring patient perspectives and preferences have gained increasing importance in clinical, regulatory and reimbursement decision-making as they can differ from HCPs. Agencies such as the Food and Drug Administration in the US and Health Technology Assessment authorities such as the National Institute for Health and Care Excellence (NICE) in the United Kingdom

are advocating the incorporation of patient preferences in the value assessment of treatments(23-26). Evidence has demonstrated that accounting for patient preferences in decision-making can positively influence treatment outcomes such as treatment satisfaction and adherence(27,28). Improved treatment adherence in turn can have positive economic implications as reported in a recent study suggesting that published economic evaluations in HS to date consistently reported treatment (dis-)continuation to be an important driver of the cost-effectiveness of HS therapies(29,30). Given the complexity of the patient journey and profound impact on quality of life, it is critical to understand key challenges from the patient perspective to bring greater awareness and understanding among healthcare providers (HCPs) who treat patients with HS(31). However, patient perspectives in the context of HS have hardly been investigated. Although the Global Survey Of Impact and Healthcare Needs project augmented the currently low understanding of unmet care needs for HS patients, further qualitative work can improve understanding of the unmet care needs and potential differences in perceptions between patients and HCPs to contribute to the optimization of HS management(16). Furthermore, no high-quality patient preference research in the form of a conjoint analysis or discrete-choice experiments (DCE) has been published with patients or HCPs in HS to date. Preliminary qualitative research aiming to identify and prioritize important treatment considerations from the perspective of patients and HCPs forms part of the process to design conjoint analyses or DCEs that are nowadays commonly used to elicit and quantify treatment preferences of patients and HCPs. Understanding and comparing perspectives of patients and HCPs may provide important insights on common misconceptions in the care provision and reveal opportunities for better harmonization in the future. The objectives of this research are twofold: [1] to reveal and prioritize the unmet care needs perceived by patients and HCPs, with the term “unmet care needs” relating to the adequacy of available treatments and disease severity or disease burden according to the characterization suggested by Vreman et al. (32); [2] to identify relevant treatment attributes and assess their relative importance in the context of HS management.

4.3. Material and methods

This study consisted of qualitative interviews with adult patients with HS and HCPs with experience treating patients with HS. The semi-structured interviews assessed the perceived unmet care needs and identified treatment attributes that patients and HCPs consider most important in the management of HS.

4.3.1. Population

The group of HCPs consisted of accredited dermatologists or surgeons experienced with HS; general practitioners (GPs) and nurses were not included due to low overall disease awareness. HCPs were identified through their presence in HS-specific literature or conference activities (European Hidradenitis Suppurativa Foundation & Symposium on Hidradenitis Suppurativa Advances) and were recruited by e-mail. Snowball sampling was deemed most appropriate for this research given the disease rarity and associated difficulties of using stricter purposeful sampling techniques(33,34). Participating patients were identified and contacted through participating HCPs or patient advocacy groups (Irish Skin Foundation, Hidradenitis Patiënten Vereniging, Hope for HS, Patientforeningen HS Danmark & Association Acne Inversa SchwAIz). Key participant inclusion criteria for patients were aged ≥18 years and a confirmed medical diagnosis of HS; participation was not restricted by HS disease severity. The study allowed participation of subjects located in Europe or North-America. All participants were made aware of the objectives of the research and provided consent to use their anonymized responses for this study. There was no compensation of any type for participation in this study. Prior to enrolment, the required sample size was estimated between 15-20 for each group based on published qualitative research with similar purpose(35,36). During the study, enrolment of participants in either group was pre-determined to be finished as soon as three consecutive interviews did not provide substantially new information (defined as no new unmet care need or treatment attribute), which is suggested by Moser & Korstjens (2018) to indicate data saturation(37-39).

4.3.2. Semi-structured interviews

A literature search in MEDLINE was conducted in May 2020 to identify important themes and select relevant items for the qualitative interview guide(40). The search revealed only seven studies in HS that were deemed relevant for development of the interview guides which were aimed to be designed in accordance with previously published patient & HCP perspectives and insights in the context of HS management(16,41-46). The interview guides (Appendix) were jointly developed by the authors, who have experience with patient preference research or are HCPs with experience in treating HS. All one-to-one interviews were conducted online using the same semi-structured interview guides, which were pilot-tested among the authors, between June 2020 and January 2021 by two male student researchers with MSc in health sciences in either English, German, Dutch, Portuguese or French language and were audio-recorded in digital format to allow accurate data processing. Both interviewers had formal academic education for the conduct of qualitative interviews, but limited practical experience, which was addressed by training of

the co-authors who are very experienced in qualitative research, by pilot-testing and by previous secondary research into patient preference studies and HS. No particular characteristic of interviewers' profiles was expected to lead to any form of bias in the conduct and analysis of the qualitative interviews. Participants were made aware of the interviewer's background at the start of the interview as no participant had familiarity with the interviewers prior to the interview. Prompts were only used to advance the discussion if the participant finished elaborating on a question. Rate of non-participation or discontinuation during the interview were noted. Due to the ongoing global COVID-19 pandemic at the time of this research, physical interviews or focus groups were not considered appropriate. All procedures performed in this study involving human participants were in accordance with the ethical standards of Maastricht University and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The first part of the interview included questions on participants' demographic information in which patients were asked about their geographic location, age, gender and disease experience, characterized by disease severity using Hurley staging, time since diagnosis and treatment experience. Participating HCPs were asked about their geographic location, medical specialization and experience treating HS patients by the number of years of treating HS patients, frequency of consulting patients with HS, disease severity range of HS patients consulted, and types of HS treatments applied(47). Categorization of participants' responses in both groups regarding their experience with HS, i.e., disease severity and type of interventions used, were not mutually exclusive as respondents could have experience with more than one classification. In the second part, to reveal the perceived unmet care needs in HS, participants were asked open-ended questions such as "*What is your view on the unmet care need in the management of HS?*" to learn about their experiences with the management of patient's condition in terms of treatment outcomes and treatment process. All participants were neutrally asked to quantify the level unmet care needs they perceive themselves on a 7-point Likert-scale (0=lowest level of unmet care needs to 7 highest level of unmet care need). Participating HCPs were additionally asked if the perceived level of unmet care need is correlated to a patient's disease severity. In the third part, treatment attributes that are influential to treatment decision-making were firstly elicited in exhaustive manner from participants and HCPs. Participants were then asked to prioritize the five most important treatment attributes out of all previously mentioned treatment attributes to elicit their relative importance.

4.3.3. Analysis and presentation of results

Descriptive statistics were used to characterize the sample and mean values with ranges were presented for continuous variables. Frequencies expressed as

percentages were presented for categorical variables. Results for identified unmet care needs and identified treatment attributes were analyzed in qualitative and quantitative manner. Coding using content analysis methods was used to analyze the qualitative interviews. For the qualitative analysis, all participants' responses were exhaustively listed and subsequently categorized; in case of conflict during the categorization process, joint decisions between the authors (including HCPs experienced in treating HS) were made. For the quantitative analyses, the proportion of participants reporting each item of unmet care need or treatment attribute was calculated and visualized in Microsoft Excel 2013. The first five interviews were jointly analyzed by two researchers to agree on a consistent analysis and classification approach for the remaining interviews which were individually analyzed. The presentation of the results adheres to reporting guidelines by Hollin et al. to enhance the transparency and trustworthiness of published qualitative methods and evidence(48). Patients' and HCPs' responses are separately presented. The unmet care needs attributes are divided into treatment outcome-specific and care process-specific items. All unmet care needs and treatments attributes mentioned by participants were either individually reported if mentioned by at least three respondents or otherwise grouped by theme. Themes to categorize unmet care needs and treatment attributes that were reported by fewer than 3 respondents were defined based on similar studies identified in the literature search or based on author experience (including HCPs experienced in treating HS). All items were listed and ranked by frequency of being reported. Relevant qualitative interview findings e.g., quotations of respondents were added in the body text to aid the interpretation of the quantitative results.

4.4. Results

4.4.1. Study sample

Interviews were conducted with a total of 28 participants, 16 HS-experienced HCPs and 12 adult patients as the pre-determined level of data saturation was achieved (no new unmet care need or treatment attribute emerging in three consecutive interviews). Interview duration was on average 30 minutes for both groups, ranging from 23 minutes to 54 minutes and 17 minutes to 45 minutes with patients and HCPs, respectively. The response rate was not possible to assess as snowballing sampling was applied, but no participant who expressed initial interest to participate refused, or discontinued participation afterwards. The sample of participating HCPs consisted of fifteen dermatologists and one surgeon. Participating HCP's experience treating HS patients ranged from 3 to 40 years with an average of 10.7 years. Participating patients were on average 41.6 (28-64) years old, mostly white/

Caucasian (93%), female (75%) and based in five European countries (83%) or United States (17%). Time since patients' medical diagnosis of HS was on average 11.2 (2-30 range) years. In addition to the demographics, Table 4-1 also depicts HCPs' and patients' experience with HS by the frequency of HS-specific consultations, disease severity spectrum, and types of interventions used. Most participants had experience across all HS severity stages defined by Hurley and had experience with the range of interventions available to treat HS, including biological therapies. The majority of both groups (>58%) indicated to have experience using off-label treatments to treat HS.

Table 4 - 1: Demographic characteristics of the study sample and their experience with HS

Characteristic	Classification	Patients (n=12)	HCPs (n=16)
Age, mean (range)	Years	41.6 (28-64)	N/A
Gender, n (%)	Female	9 (75)	2 (12)
Race, n (%)	White or Caucasian	11 (92)	N/A
	Black or African American	1 (8)	N/A
Location, n (%)	Europe	10 (83)	14 (88)
	North-America	2 (17)	2 (12)
Experience with HS, mean (range)	Years	11.2 (2-30)	10.7 (3-40)
Consultations for HS*, n (%)	0 – 9	8 (67)	2 (12)
	10 – 29	4 (33)	9 (56)
	30 – 50	-	3 (19)
	>50	-	2 (12)
Disease severity, n (%)	Mild	11 (92)	16 (100)
	Moderate	10 (83)	14 (88)
	Severe	8 (67)	14 (88)
Interventions used, n (%)	Minor surgery	9 (75)	13 (81)
	Excisional surgery	7 (58)	7 (44)
	Antibiotic treatment	10 (83)	16 (100)
	Biological treatment	6 (50)	14 (87)
	Off-label treatment	7 (58)	13 (81)

*Note: *per week (HCPs) and per year (patients). HCP: health care professional; N/A: not applicable; HS: hidradenitis suppurativa.*

4.4.2. Unmet care needs

A total of 16 unmet care themes were identified through interviews and classified to be either treatment outcome-related (8) and care process-related (8). Participating HCPs and patients most frequently reported the negative QoL as unmet care need, which patients explained to be driven by the lacking improvement of general or skin-specific QoL, productivity levels, fatigue, leisure activities, mental health, intimacy issues and social life including stigmatization of available treatment options.

> "*I have made career choices and avoided greater work responsibilities just to accommodate my HS because I cannot have others relying on my ability to work.*" US patient, female, age 38, white skin color with moderate HS.

> "*I was unable to walk on bad days prior to receiving a series of excisional surgeries combined with biologic therapy ten years ago. When the therapies worked, I got back control over my life and underwent a huge life transformation, but in the past 6 months it started going wrong again after many good years and I suffered from new lesions in new body areas.*" Irish patient, male, age 46, white skin color with moderate HS.

Poor effectiveness of available interventions, in particular low response rate or likelihood of response was emphasized by ten patients and fourteen HCPs, with the latter group frequently noting that current interventions do not provide sufficient patient satisfaction and durable inflammation control.

> "*It's a huge unmet need that the available treatments often lose effect over time which is aggravated by the limited number of alternatives to switch patients to.*" US Dermatologist, male, with over 10 years of experience treating mild to severe HS patients.

Inadequate pain management was perceived by both groups as an important unmet care need that is often overlooked due to prioritizing improvement in visual or inflammatory signs of HS.

> "*Pain management is non-existent despite it having the biggest impact on my quality of life. A lot of dermatologists don't even ask you if you are in pain or how you are managing it because it doesn't even occur to them that HS may be painful.*" US patient, female, age 39, white skin color with severe HS.

Eleven HCPs highlighted the low durability of treatment effectiveness of current interventions and the inability to halt disease progression in patients, with some in particular concerned for patients at risk of progression from mild to moderate or severe stages of HS. Eight respondents in both groups stated concerns regarding the side-effects of available antibiotic- or biological therapies, drug-to-drug interactions and the high burden of undergoing surgery. Perceptions of unmet care needs were mostly similar between patients and HCPs, though patients more frequently emphasized the inability of current care options to improve visual appearance or prevent scarring. Table 4-2 presents the unmet care needs relating to treatment outcomes, including respondents' characterization of each unmet need and the frequency of being reported.

Table 4 - 2: Identified unmet care needs related to treatment outcomes

Treatment outcome-related unmet care need	Respondents' characterization of unmet care need	Patients (n=12)	HCPs (n=16)
QoL impact	Lacking improvement of general or skin-specific QoL; mental health; productivity; social life; intimacy issues; lifestyle restrictions	11 (92)	14 (88)
Effectiveness	Insufficient control or reduction of lesions, nodules or draining fistulas; lacking effect on inflammation, flares, or other symptoms; low treatment response rate, efficacy, or likelihood of response; insufficient patient satisfaction	10 (83)	14 (88)
Pain control	Inadequate pain reduction, control, or improvement	9 (75)	11 (69)
Duration of effect	Poor maintenance of effect; low durability of effect; frequent loss of response or disease recurrence	7 (58)	11 (69)
Side-effects	Concerning antibiotics or biologic side effects; drug-to-drug interactions; comorbidity implications; life implications of surgery	8 (67)	8 (50)
Disease progression	Inadequate halting of disease progression or worsening of disease	5 (42)	9 (56)
Skin appearance	Dissatisfying visual or odor appearance of skin affected by disease or scarring	7 (58)	4 (25)
Time to onset	Slow onset of effect or treatment response; difficult early prediction of later treatment success	4 (33)	5 (31)

Note: Data are presented as n (%) and sorted by decreasing frequency of being mentioned. HCP: health care professional; QoL: quality of life.

Table 4-3 portrays the perceived unmet care needs relating to the care process; including respondents' characterization of each unmet care need and the frequency of being reported. Patients frequently reported delays in receiving a correct medical diagnosis, thought to be caused by low disease awareness in GPs and dermatologists. Fourteen HCPs confirmed this issue by explaining that patients often experience multiple unsuccessful referrals, wrong diagnoses and ineffective treatment intimations until HS is correctly diagnosed by a specialist.

"It took me twenty years to get a correct diagnosis and I had to see a lot of specialists before I found someone in Ireland who is familiar with this condition." Irish patient, age 46, male, white skin color with moderate HS.

Fragmentation of care delivery concerned ten HCPs who admitted suboptimal collaboration and patient follow-up between GPs, dermatologists, surgeons, pharmacists and nurses. Eight patients shared concerns regarding the insufficient wound care guidance received by nurses and HCPs due to insufficient education provided or guidance published.

"There is not nearly enough support for the detrimental mental aspects that are involved in living with HS as it is swept under the rug in the United States." US patient, female, age 39, white skin color with severe HS.

Many patients further highlighted the very high costs for wound dressings and skin care products since reimbursement is often partially or completely lacking in the US and some European countries. Costs of medical treatments and consultations were perceived as problematic by US patients while most European respondents reported sufficient medication reimbursement. However, difficulty accessing HS specialists due to waiting times or geographic distance was reported by seven patients across both geographies.

"It usually takes me 8 months to see my specialist for which I also have extremely high co-payments. Another frustration is getting the care coordinated between my primary care provider and my specialist because I have multiple conditions whose therapies sometimes conflict each other." US patient, age 38, female, white skin color white with severe HS.

"HS is a disease that costs me a lot of money. While out-of-pocket costs for medical interventions are manageable, the specific products that I need to treat my skin and wounds not always reimbursed and have costed me a lot of money over the long course of my disease." French patient, age 44, female, white skin color with moderate HS.

Such access barriers were of particular concern for patients during disease flaring as patients felt most emergency departments (EDs) are unaware of HS and cannot provide appropriate urgent or emergent care on such occasions.

> *"I see a frequently underrecognized unmet need in the limited options to treat patients with mild forms of HS. Current treatment options together with delays in diagnosis don't allow us to prevent new inflammation in these patients with mild HS which to me is a great treatment opportunity missed."* Dermatologist in the Netherlands, male, with over 10 years of experience treating mild to severe HS patients.

Patients and HCPs scored the level of perceived unmet care needs on a 7-point Likert scale with 4.5 (2-6) and 5.5 (3-7), respectively. Eleven HCPs confirmed greater unmet care needs with increasing disease severity, whilst two were more concerned about the lack of effective interventions to adequately treat mild HS patients to prevent disease progression.

Table 4 - 3: Identified unmet care needs related to care process

Care process-related unmet care need	Respondents' characterization of unmet care need	Patients (n=12)	HCPs (n=16)
Timely diagnosis	Delayed, wrong or no diagnosis provided	9 (75)	14 (88)
Disease awareness	Poor general awareness or knowledge of HS; inadequate care provision until correct diagnosis	11 (92)	11 (69)
Healthcare system settings	Inadequate healthcare system care set-up; lacking care integration, follow-up or self-care guidance; long geographic distance to HS specialist; care inefficiencies due to fragmented care provision	6 (50)	10 (63)
Wound care guidance	Insufficient patient and nurse education on HS-specific wound care; lacking published guidance or information	8 (67)	5 (31)
Treatment selection process	Lack of shared decision-making, patient involvement	6 (50)	9 (56)
Access to HS specialists	Long waiting times; high number of referrals to consult HS specialist	7 (58)	4 (25)
Wound care costs	High cost for wound dressings, bandages, supplies or skin/hygiene products; limited reimbursement or coverage of wound care supplies	8 (67)	1 (6)
Treatment costs	High out-of-pocket treatment costs; low coverage or reimbursement; limited possible choice of treatment	4 (33)	5 (31)

Note: Data are presented as n (%) and sorted by decreasing frequency of being mentioned. HCP: health care professional; HS: hidradenitis suppurativa.

3.4.3. Treatment attributes

Thirteen treatment attributes were identified which are presented with respondents' characterization and frequency of being reported in Table 4-4. All patients expressed the importance of treatments leading to an improvement in QoL. More specifically, nine patients expected improvements in productivity levels (incl. education or work), eight patients expressed expectations for treatments to improve their mental health (incl. anxiety, depression, stigmatization or self-realization) and social life (incl. leisure activities or private relationships) and five patients emphasized the importance of reducing fatigue.

> *"It would be great if future treatments could better reduce my pain and help me break away from this vicious circle in which my HS symptoms negatively impact my mental health and social life which in turn negativity influence my condition."* Swiss patient, age 28, female, white skin color with moderate HS.

Likelihood of response to be achieved was the second most frequently desired treatment attribute by both groups. Patients reported more frequently than HCPs the importance of treatments being able to reduce pain, improve skin appearance or odor, or leading to avoidance of surgery.

> *"If nothing works, you are having a surgery and have to undergo weeks and weeks and weeks of recovery, only for it (HS) to recur in the same place quite quickly. A big thing would be if future treatments can stop it (HS) from coming back, that would be amazing."* Irish patient, age 37, female, white skin color with severe HS.

HCPs more frequently than patients cited the importance of treatments being able to control inflammation (incl. nodules, lesions and draining fistulas), halt disease progression and show fast onset of action enabling earlier treatment success prediction.

> "*We need medicines that respond in more patients and have a more profound and consistent effect."* US Dermatologist, male, with over 10 years of experience treating mild to severe HS patients.

Table 4 - 4: Identified treatment attributes

Treatment attribute	Respondents' characterization of treatment attribute	Patients (n=12)	HCPs (n=16)
QoL improvement	Mental health improvement (incl. improved depression, anxiety, psychological problems, mental stability, stigmatization, confidence or self-realization); greater productivity (incl. education and work); social life (incl. leisure activities, sports, private relationships, travel or family activities); fatigue improvement	12 (100)	13 (81)
Effectiveness	Likelihood of response; response rate; chance of response; efficacy	10 (83)	13 (81)
Treatment convenience	Method, location or frequency of administration; contact to healthcare personal	9 (75)	13 (81)
Duration of effect	Response maintenance; duration of effect; avoidance of disease recurrence	10 (83)	10 (63)
Long-term treatment safety	Reduced long-term treatment side effects; reduced drug-to-drug interactions; avoidance of comorbid complexities	8 (67)	10 (63)
Pain reduction	Pain reduction, control or improvement	10 (83)	7 (44)
Skin appearance	Improvement of scarring, visual or odor appearance	10 (83)	7 (44)
Surgery avoidance	Avoidance of surgery	9 (75)	7 (44)
Immunological control	Immunological stability; control of inflammation; avoidance of flares; reduction of nodules/lesions/draining fistulas	5 (42)	9 (56)
Time to effect onset	Time to response; speed of response; predictability of response	5 (42)	8 (50)
Disease progression	Avoiding disease progressing or halting of disease progression	3 (25)	9 (56)
Treatment costs	Low patient out-of-pocket cost; adequate coverage or reimbursement	5 (42)	7 (44)
Treatment satisfaction	Satisfaction with treatment	0 (0)	6 (38)

Note: Data are presented as n (%) and sorted by decreasing frequency of being mentioned. HCP: health care professional; QoL: quality of life; HS: hidradenitis suppurativa.

When participants were asked to limit their previously mentioned treatment attributes to the five most important ones, differences in priorities between patients and HCPs became apparent (Figure 4-1). Pain reduction was revealed to have the highest probability of being cited within the five most important attributes by patients, followed by treatment effectiveness. HCPs prioritized effectiveness,

immunological control and QoL improvement. Improvements in visual appearance or odor, surgery avoidance and mental health were prioritized by patients but not at all by HCPs.

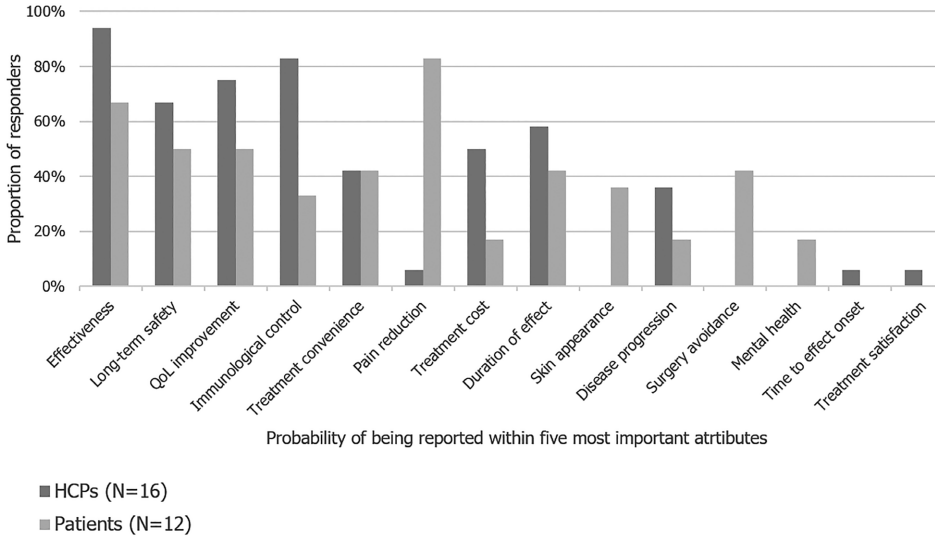


Figure 4 - 1: Probability of treatment attributes being mentioned as one of the five most important
Note: HCP: health care professional; QoL: quality of life.

4.5. Discussion

With evidence on patients' and HCP's perspectives in the management of HS of patients' being scarce to date, this research revealed novel insights on important unmet care needs and treatment considerations from patients and HCPs through the conduct of qualitative interviews. The overall perception of unmet care needs was high in both groups and related to treatment outcomes or care process-related issues. The inability of currently available therapies to show satisfying levels effectiveness to improve QoL and HS pain was revealed to drive the treatment outcome-related unmet care needs. This is also confirmed by the high number of respondents in both groups reporting experience with "off-label" treatments to manage HS. Both groups were highly concerned about delays in diagnosis, mostly attributable to low level of disease awareness, leading patients to undergo many unsuccessful referrals and treatment initiations during which the disease can progress; this has been defined as a global problem(17). Even after a correct diagnosis, both groups emphasized significant inefficiencies in the HS management process due to fragmented care delivery, insufficient HS-specific education, inadequate wound care guidance and access barriers to HCPs with expertise in HS. The results highlight that for US respondents, costs to the individual are an important concern, which is not surprising given the US multi-payer health care system. However, access barriers to HS-specialist due to long waiting times and geographic distance were also reported by respondents outside the US which is considered problematic because it leads to HS patients visiting EDs for expensive and inefficient treatment and pain relief as Taylor et al. alert(49). The views of both groups in our study on unmet care needs were mostly similar, with the exception of patients reporting more concerns around the skin appearance (visual & odor) and guidance on wound care and cost of wound care which HCPs did not emphasize as strongly.

Unsurprisingly, given the high unmet care needs caused by the limited number of effective treatments available, patients and HCPs prioritized improvements in effectiveness and QoL over safety or convenience as treatment attributes. Improvement in HS pain, appearance of skin and avoidance of surgery were more frequently considered by patients as the most important treatment attributes, while HCPs more frequently pointed out improved immunological control (reduced level of inflammation) and avoidance of disease progression defined by patients' skin manifestations(47). There were little to no controversies in the respondents' statements with the exception of some HCPs seeing greatest need to prevent disease progression more successfully at early stages with more effective treatments, while others emphasized the need to have more effective

treatment options for more severe patients that had already exhausted the limited treatment options available. The pre-specified target level of data saturation (three consecutive interviews with no new unmet care need or treatment attribute emerging) was achieved with a sample size close to those what can be observed in similar qualitative research(35,36). A greater number of interviews with HCPs (n=16) than with patients (n=12) was needed which could indicate the responses from HCPs to be more heterogenous than those of patients. A study by Garg et al. eliciting the identifying care needs of 1299 participants in Europe and North-America also revealed that participants were most concerned about delayed diagnoses, HS-related pain, access to dermatology and extreme QoL impact(16). Authors of the HIdradenitis SuppuraTiva cORe outcomes set International Collaboration tried to address the current lack of consensus on outcome measures and agreed on pain, physical signs, HS-specific quality of life, global assessment and disease progression to be consistently assessed which are similar to domains of unmet care identified in our study(50,51). The frequently reported issues in qualitative research on respondents' differing expressions of similar meanings have been addressed in this study by a prior literature search to inform the design of interview guides and by exhaustive listing and subsequent classification of all items reported by participants. However, it cannot fully be dismissed that some unmet need categories or treatment attributes are not mutually exclusive. For example, unmet needs relating to treatment effectiveness can also be closely associated with QoL improvement or treatment satisfaction, Table 4-2 presents in detail which aspects of each item were mentioned by the respondents. Although our study followed good research practices, some limitations may exist. First, potential selection bias and limitations in generalizability due to the sample size may have impacted the study despite respondents' statements becoming repetitive after approximately ten interviews in each group indicating data saturation. The study design and pre-determined sample size requirements were targeted to identify strong trends between participants' profiles. Second, GPs and nurses, whose experiences could have brought additional perspectives on the HS patient journey, were not interviewed due the awareness of HS in these groups reportedly being too low. Third, while this study was able to reveal interesting insights from respondents across multiple countries, a more focused recruitment of participants from only one country would have potentially allowed to reveal potential flaws of one particular healthcare system in greater detail. Finally, the conduct of physical focus groups could have resulted in insightful exchanges between participants but were not feasible due to the ongoing COVID-19 pandemic at time of this research. This study further underpinned that qualitative research is a beneficial step prior to designing quantitative preference elicitation instruments due to familiarization with the target

population and its preferences and supporting attribute/level refinement. Our study identified important opportunities for future research to better understand the preferences of patients and HCPs in the management of HS, preferably using quantitative preference elicitation methods. The prioritization exercise of treatment attributes enabled us to identify a range of patient- and HCP-relevant attributes for potential inclusion in future DCEs. Further research is needed to determine which of these attributes are most appropriate for a DCE in HS to ensure cognitive burden for participants is manageable(52). Wider contextual issues (delay in diagnosis, access to specialist, fragmented care, wound care issues) were revealed to be of importance to patients and HCPs that require further consideration in the design of a future DCEs; this could be done by testing treatment effects attributes more holistically to account for their impact on the care continuum such as e.g. reduction of surgery, associated burden of wound care and number of follow-up visits required, instead of only testing different levels of treatment effect expressed in plain response rates. Assessing the trade-offs and relative importance of treatment attributes in larger samples using a quantitative elicitation approach will allow greater understanding of influential factors of respondents' profile and improve generalizability of findings with the aim to improve future clinical-, regulatory-, and reimbursement decision-making to reduce the currently high level of unmet care needs in HS.

4.6. Conclusions

This study revealed that current HS treatment options and care processes leave patients and HCPs with a high level of unmet need. HCPs and patients have mostly similar views on unmet care needs such as low effectiveness and pain control. Patients emphasized the challenges relating to access to HS specialists and issues relating to guidance and costs of wound care. Treatment effectiveness outcomes were considered as the most important treatment attributes by both groups. Yet our study highlighted important care process-related considerations that may impact respondents' preferences which should be accounted for in future DCE study designs.

4.7. References

1. Phan K, Charlton, O., Smith, SD. Global prevalence of hidradenitis suppurativa and geographical variation—systematic review and meta-analysis. Biomedical Dermatology 2020;4.
2. Jemec GB. Clinical practice. Hidradenitis suppurativa. N Engl J Med 2012;366:158-64.
3. 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.
4. Kirsten N, Petersen J, Hagenstrom K, Augustin M. Epidemiology of hidradenitis suppurativa in Germany - an observational cohort study based on a multisource approach. J Eur Acad Dermatol Venereol 2020;34:174-179.
5. Zouboulis CC, Del Marmol V, Mrowietz U, Prens EP, Tzellos T, Jemec GB. Hidradenitis Suppurativa/Acne Inversa: Criteria for Diagnosis, Severity Assessment, Classification and Disease Evaluation. Dermatology 2015;231:184-90.
6. Cartron A, Driscoll MS. Comorbidities of hidradenitis suppurativa: A review of the literature. Int J Womens Dermatol 2019;5:330-334.
7. Shavit E, Dreiher J, Freud T, Halevy S, Vinker S, Cohen AD. Psychiatric comorbidities in 3207 patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol 2015;29:371-376.
8. Onderdijk AJ, van der Zee HH, Esmann S et al. Depression in patients with hidradenitis suppurativa. J Eur Acad Dermatol Venereol 2013;27:473-8.
9. Sartorius K, Emtestam L, Jemec GB, Lapins J. Objective scoring of hidradenitis suppurativa reflecting the role of tobacco smoking and obesity. Br J Dermatol 2009;161:831-9.
10. Esmann S, Jemec GB. Psychosocial impact of hidradenitis suppurativa: a qualitative study. Acta Derm Venereol 2011;91:328-32.
11. Fleischer AB, Jr. Characterization of obesity rates for dermatologic ambulatory office visits to United States physicians. J Dermatolog Treat 2017;28:181-185.
12. Lim ZV, Oon HH. Management of Hidradenitis Suppurativa in Patients with Metabolic Comorbidities. Ann Dermatol 2016;28:147-51.
13. Gooderham M, Papp K. The psychosocial impact of hidradenitis suppurativa. J Am Acad Dermatol 2015;73:S19-22.
14. Riis PT, Vinding GR, Ring HC, Jemec GB. Disutility in Patients with Hidradenitis Suppurativa: A Cross-sectional Study Using EuroQoL-5D. Acta Derm Venereol 2016;96:222-6.
15. Kokolakis G, Wolk K, Schneider-Burrus S et al. Delayed Diagnosis of Hidradenitis Suppurativa and Its Effect on Patients and Healthcare System. Dermatology 2020;236:421-430.
16. 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;82:366-376.
17. Saunte DM, Boer J, Stratigos A et al. Diagnostic delay in hidradenitis suppurativa is a global problem. Br J Dermatol 2015;173:1546-9.
18. Andersen RK, Jemec GB. Treatments for hidradenitis suppurativa. Clin Dermatol 2017;35:218-224.

19. Goldburg SR, Strober BE, Payette MJ. Hidradenitis suppurativa: Current and emerging treatments. J Am Acad Dermatol 2020;82:1061-1082.
20. van Straalen KR, Schneider-Burrus S, Prens EP. Current and future treatment of hidradenitis suppurativa. Br J Dermatol 2020;183:e178-e187.
21. Schlapbach C, Hanni T, Yawalkar N, Hunger RE. Expression of the IL-23/Th17 pathway in lesions of hidradenitis suppurativa. J Am Acad Dermatol 2011;65:790-798.
22. Willems D, Rolleri, B., Pansar, I., Kroi, F. & Hashim, M. . A Systematic Literature Review and Early Network Meta-Analysis of Current and Future Treatments for Moderate to Severe Hidradenitis Suppurativa. Value Health 2020;23.
23. Ho MP, Gonzalez JM, Lerner HP et al. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc 2015;29:2984-93.
24. G U. NICE to research patient preferences in HTA. PharmaTimes 2016.
25. Sain N, Willems D, Charokopou M, Hiligsmann M. The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments. Curr Med Res Opin 2020;36:1257-1275.
26. Danner M, Hummel JM, Volz F et al. Integrating patients' views into health technology assessment: Analytic hierarchy process (AHP) as a method to elicit patient preferences. Int J Technol Assess Health Care 2011;27:369-75.
27. Umar N, Schaarschmidt M, Schmieder A, Peitsch WK, Schollgen I, Terris DD. Matching physicians' treatment recommendations to patients' treatment preferences is associated with improvement in treatment satisfaction. J Eur Acad Dermatol Venereol 2013;27:763-70.
28. Thorneloe RJ, Bundy C, Griffiths CE, Ashcroft DM, Cordingley L. Nonadherence to psoriasis medication as an outcome of limited coping resources and conflicting goals: findings from a qualitative interview study with people with psoriasis. Br J Dermatol 2017;176:667-676.
29. Jevtic T, Bukumiric Z, Jankovic SM. Effects of treatment adherence on clinical and economic outcomes in patients with psoriasis. Med Glas (Zenica) 2013;10:106-12.
30. Willems D, Charokopou M, Evers S, Hiligsmann M. Early health economic modelling for a treatment candidate in hidradenitis suppurativa. J Med Econ 2020:1-9.
31. Soekhai V, de Bekker-Grob EW, Ellis AR, Vass CM. Discrete Choice Experiments in Health Economics: Past, Present and Future. Pharmacoeconomics 2019;37:201-226.
32. Vreman RA, Heikkinen I, Schuurman A et al. Unmet Medical Need: An Introduction to Definitions and Stakeholder Perceptions. Value Health 2019;22:1275-1282.
33. Kalton G, Anderson, D. Sampling rare populations. Journal of the Royal Statistical Society: Series A (General) 1986;149:65-82.
34. Palinkas LA, Horwitz SM, Green CA, Wisdom JP, Duan N, Hoagwood K. Purposeful Sampling for Qualitative Data Collection and Analysis in Mixed Method Implementation Research. Adm Policy Ment Health 2015;42:533-44.
35. Danner M, Vennedey V, Hiligsmann M, Fauser S, Stock S. Focus Groups in Elderly Ophthalmologic Patients: Setting the Stage for Quantitative Preference Elicitation. Patient 2016;9:47-57.
36. Somers C, Chimonas S, McIntosh E, Kaltenboeck A, Briggs A, Bach P. Using Nominal Group Technique to Identify Key Attributes of Oncology Treatments for a Discrete Choice Experiment. MDM Policy Pract 2019;4:2381468319837925.

37. Francis JJ, Johnston M, Robertson C et al. What is an adequate sample size? Operationalising data saturation for theory-based interview studies. Psychol Health 2010;25:1229-45.
38. Turner-Bowker DM, Lamoureux RE, Stokes J et al. Informing a priori Sample Size Estimation in Qualitative Concept Elicitation Interview Studies for Clinical Outcome Assessment Instrument Development. Value Health 2018;21:839-842.
39. Moser A, Korstjens I. Series: Practical guidance to qualitative research. Part 3: Sampling, data collection and analysis. Eur J Gen Pract 2018;24:9-18.
40. Bridges JF, Hauber AB, Marshall D et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health 2011;14:403-13.
41. Tracey EH. Don't forget these 5 things when treating hidradenitis suppurativa. Cutis 2019;104:E27-E28.
42. Fisher S, Jehassi A, Ziv M. Hidradenitis suppurativa on Facebook: thematic and content analyses of patient support group. Arch Dermatol Res 2020;312:421-426.
43. Golbari NM, Porter ML, Kimball AB. Online communications among hidradenitis suppurativa patients reflect community needs. J Am Acad Dermatol 2019;80:1760-1762.
44. Gulliver W, Landells IDR, Morgan D, Pirzada S. Hidradenitis Suppurativa: A Novel Model of Care and an Integrative Strategy to Adopt an Orphan Disease. J Cutan Med Surg 2018;22:71-77.
45. Hamzavi IH, Sundaram M, Nicholson C et al. Uncovering burden disparity: A comparative analysis of the impact of moderate-to-severe psoriasis and hidradenitis suppurativa. J Am Acad Dermatol 2017;77:1038-1046.
46. Bettoli V, Pasquinucci S, Caracciolo S et al. The Hidradenitis suppurativa patient journey in Italy: current status, unmet needs and opportunities. J Eur Acad Dermatol Venereol 2016;30:1965-1970.
47. Horvath B, Janse IC, Blok JL et al. Hurley Staging Refined: A Proposal by the Dutch Hidradenitis Suppurativa Expert Group. Acta Derm Venereol 2017;97:412-413.
48. Hollin IL, Craig BM, Coast J et al. Reporting Formative Qualitative Research to Support the Development of Quantitative Preference Study Protocols and Corresponding Survey Instruments: Guidelines for Authors and Reviewers. Patient 2020;13:121-136.
49. Taylor MT, Orenstein LAV, Barbieri JS. Pain Severity and Management of Hidradenitis Suppurativa at US Emergency Department Visits. JAMA Dermatol 2021;157:115-117.
50. Thorlacius L, Garg A, Ingram JR et al. Towards global consensus on core outcomes for hidradenitis suppurativa research: an update from the HISTORIC consensus meetings I and II. Br J Dermatol 2018;178:715-721.
51. 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;179:642-650.
52. Hiligsmann M, Dellaert BG, Dirksen CD et al. Patients' preferences for osteoporosis drug treatment: a discrete-choice experiment. Arthritis Res Ther 2014;16:R36.

4.8. Appendix

Interview guide for HCPs

Background:

1) What is your current job title & role?
2) Do you have experience treating patients diagnosed with HS?
3) How many years of experience do you have treating HS patients?
4) What is the spectrum of disease severity of HS that you have experience treating?

a. Options: mild, moderate, severe (Hurley staging as possible metric)

5) What is the spectrum of treatment interventions you perform on HS patients?

a. Options: minor surgery, excisional surgery, antibiotic treatment, biological treatment, off-label treatment

6) How many consultations on average per week with HS patients would you estimate to have?

a. Options : 0-5, 5-10, 10-30, 30-50, 50+

Unmet care needs:

1) What is your view on the unmet care need in the management of HS? Please be exhaustive related to treatment outcomes and care process
2) On a 7-point Likert scale with 1 being “no unmet needs at all” and 7 being “greatest level of unmet needs”, what do you believe is the level of unmet needs in HS from a HCP perspective (if known)? Please explain your rating.
3) Do you believe this unmet need is different from a patient perspective? If yes, how?

Treatment attributes:

1) Which treatment attributes influence your treatment decision-making as HCP? Please be exhaustive.
2) Considering the treatment attributes you recently mentioned, please limit yourself to the five most important attributes for you in medical decision-making

Interview guide for patients

Background:

1) What is your gender?
2) What is your age?
3) What is your ethnicity?
4) Did you have a medical diagnosis of HS? If yes, how many years ago
5) Which severity stages of HS have you experienced yourself?
6) What is the spectrum of treatment interventions you have experienced yourself?

a. Options: minor surgery, excisional surgery, antibiotic treatment, biological treatment, off-label treatment

Unmet care needs:

1) What is your view on the unmet care need in the management of HS? Please be exhaustive related to treatment outcomes and care process
2) On a 7-point Likert scale with 1 being "no unmet needs at all" and 7 being "greatest level of unmet needs", what do you believe is the level of unmet needs in HS from a patient's perspective (if known)? Please explain your rating.

Treatment attributes:

1) Which treatment attributes or treatment characteristics would influence your treatment decision-making as patient? Please be exhaustive.
2) Considering the treatment attributes you recently mentioned, please limit yourself to the five most important attributes for you in treatment decision-making

5

Patient preferences in the management of hidradenitis suppurativa: results of a multinational discrete-choice experiment in Europe

Chapter 5 was informed by:
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5.1. Abstract

Background: Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease that can lead to substantial reduction in quality of life. Recent studies revealed high levels of unmet care needs of patients with HS, but their preferences in treatment decision-making have scarcely been investigated.

Methods: A discrete-choice experiment (DCE) was conducted with adult HS patients in Europe to reveal which treatment attributes are most important when making treatment decisions. Participants were presented with 15 sets of two treatment options and asked for each to choose the treatment they preferred. The treatments were characterised by six attributes informed by prior literature review and qualitative research: effectiveness, pain reduction, duration of treatment benefit, risk of mild adverse event (AE), risk of serious infection, and mode of administration. A random parameters logit model was used to estimate patients' preferences with additional subgroup- and latent class models used to explore any differences in preferences across patient groups.

Results: 219 adult patients with HS were included in the analysis (90% women, mean age 38 years). For all six treatment attributes, significant differences were observed between levels. Given the range of levels of each attribute, the most important treatment attributes were effectiveness (47.9%) followed by pain reduction (17.3%), annual risk of mild AE (14.4%), annual risk of serious infection (10.3%), mode of administration (5.3%) and duration of treatment benefit (4.8%). Higher levels of effectiveness, namely 75% or 100% reduction of abscess and inflammatory nodule count were preferred over levels of effectiveness primarily investigated in randomised clinical trials (RCTs) of HS (50% reduction). Results were largely consistent across subgroups and three latent class groups were identified.

Conclusions: This study revealed the most important treatment characteristics for patients with HS which can help inform joint patient-physician decision-making in current management of HS. Designing future HS treatments according to stated preferences, namely, to offer higher levels of effectiveness and pain improvement without higher risks of adverse events may increase patients' treatment concordance and lead to improved disease management outcomes.

5.2. Introduction

Hidradenitis suppurativa (HS), is a chronic inflammatory skin disease that is characterised by recurrent nodules, tunnels, and scarring in flexural skin locations leading to a severe reduction in quality of life(1-3). The prevalence of HS is estimated between 0.03–1% with onset at an average age of 22 years(4). Low disease awareness and associated misdiagnoses as well as under-reporting by patients due to shame, and embarrassment have contributed to substantial delays in diagnosis, reported to be on average between 7–10 years(5-7). The course of disease is often unpredictable, which can be challenging for patients and healthcare professionals (HCPs) in the management of HS(8). Antibacterial treatments are recommended for mild-to-moderate HS with anti-inflammatory treatments suggested for more severe HS. Surgery is commonly used to treat skin tunnels, scars, and anatomic changes which have manifested(9). Adalimumab is currently the only approved biologic therapy in the European Union, UK, and US for patients with moderate-to-severe HS(10). Currently available treatment options are known to only allow one-third of treated patients to experience remission of their disease and almost half of treated patients with HS remain dissatisfied due to poor efficacy, undesirable adverse effects, inconvenience, or invasiveness(7,11-13). Additional treatment options are in development for HS including small molecule or biological treatments, with bimekizumab and secukinumab (both monoclonal antibodies against interleukin-17) recently reporting positive phase III studies(10,14-19). As such novel therapies may offer different treatment outcomes, the understanding of patient perspectives and treatment preferences becomes more important(20). Although recent studies began to reveal the unmet care needs and treatment desires from patients and HCPs in HS, there is a paucity of quantitative patient preference research as no published discrete-choice experiment (DCE) in HS was identified at time of this research(7,11,21). Such evidence could inform future regulatory- and reimbursement decision-making as authorities such as the US Food and Drug Administration and the National Institute for Health and Care Excellence in England(22) by advocating the incorporation of patient preferences in the value assessment of treatments(22,23). Accounting for patient preferences in clinical decision-making may further positively influence treatment outcomes such as treatment satisfaction and concordance which in turn can lead to positive health and economic implications(20,24-29). This study was therefore designed to provide novel insights into treatment attributes patients with HS consider most important when making disease management decisions by quantifying their preferences using a DCE.

5.3. Materials and methods

5.3.1. Qualitative research for selection of treatment attributes

In the absence of previously published DCEs in HS at time of this research, qualitative interviews were conducted with adult patients diagnosed with HS (N=12) and HCPs (N=16) experienced in treating HS to elicit a comprehensive list of influential treatment attributes to be included in this DCE(21,30). All interviews were conducted online using the same semi-structured interview guide which asked participants about their unmet care needs and experiences managing the disease. Participants were subsequently asked what they liked and did not like about current and previous treatments, what the most important treatment factors are as well as which areas of disease management future treatments should improve. The number of attributes in this DCE was targeted between 4 and 7 to be in line with previous DCEs and to be cognitively manageable for participants(26). Based on the insights of the qualitative interviews, the following six treatment attributes were considered most relevant for this DCE (in no particular order): [a] effectiveness on reducing the number of painful, inflammatory lesions, [b] reduction of pain, [c] duration of treatment benefit, [d] risk of mild side effects, [e] risk of serious infection and [f] mode of administration. Detailed descriptions of the methodology and findings from the qualitative interviews were previously reported(21).

5.3.2. Selection of attribute levels

The different levels of the treatment attributes were informed by reviewing the literature and confirmed with clinicians. Published clinical trial data on available and investigational HS treatments was deemed most appropriate to select the ranges of 'effectiveness' (percent reduction of the number of painful, inflammatory lesions)(16,31). The levels of 'pain reduction', which was one of the most reported unmet needs in previous research, were informed by published evidence on clinically meaningful pain improvement thresholds in HS and DCEs in other chronic diseases(32-35). The different levels of 'duration of treatment benefit' were based on studies of currently available treatments and recommendations of previous DCEs(36-38). For the safety attributes 'risk of mild adverse event' (AE) and 'risk of serious infection' the levels were informed by AE data of available and investigational therapies in HS or other chronic inflammatory diseases(16,28,31,39,40). For 'mode of administration', the three most common administration options of available and investigational HS treatments were selected, namely a bi-weekly subcutaneous injection, a monthly intravenous injection or daily oral pill(10,16,41). The final attributes and levels are shown in Table 5-1, and an example of a choice question in the DCE is shown in Figure 5-1.

Table 5 - 1: Attributes and levels included in the DCE questions

Attribute	Attribute description	Attribute levels
Effectiveness	Percentage reduction of the number of painful, inflammatory lesions on your skin	– 25% – 50% – 75% – 100%
Pain reduction	Reduction of pain (on a scale ranging from 0 to 10)	– Small pain relief (1-point) – Moderate pain relief (3-points) – Almost complete pain relief (6-points)
Duration of treatment benefit	The duration during which the treatment provides the proposed effectiveness and pain relief.	– 6 months – 12 months – 24 months
Risk of mild side effect	Annual risk of experiencing mild side effect while taking the treatment.	– 100 people out of 1000 (10%) – 300 people out of 1000 (30%) – 500 people out of 1000 (50%)
Risk of serious infection	Annual risk of experiencing a serious infection while taking the treatment.	– 1 person out of 1000 (0.1%) – 10 people out of 1000 (1%) – 30 people out of 1000 (3%)
Mode of administration	How the treatment is provided to you	– Oral tablet, once every day – Subcutaneous injection, once every 2 weeks at home or in a clinic – Intravenous injection, once every 4 weeks in a clinic or hospital setting

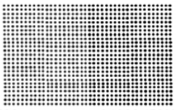
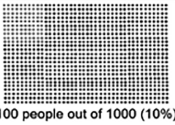
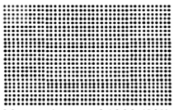
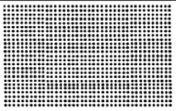
	Treatment A	Treatment B
Effectiveness Percentage reduction of the number of painful, inflammatory lesions on your skin.	 50% Reduction	 25% Reduction
Pain Reduction of pain	**Almost complete pain relief** 6-point reduction on a scale of 0–10	**Moderate pain relief** 3-point reduction on a scale of 0–10
Duration of treatment benefit The duration during which the treatment provides the outlined benefits	24 Months	12 Months
Risk of mild side effect Annual risk to experience a mild side effect	 500 people out of 1000 (50%)	 100 people out of 1000 (10%)
Risk of serious infection Annual risk to experience a serious infection	 30 people out of 1000 (3%)	 1 person out of 1000 (0.1%)
Mode of administration How the treatment is provided to you	 1 subcutaneous injection every 2 weeks	 1 pill every day
Which treatment do you prefer?	Treatment A ☑	Treatment B ☐

Figure 5 - 1: Example Choice Task

5.3.3. Survey development and conduction

The DCE was developed according to the guidelines provided by the ISPOR Good Research Practice for Conjoint Analysis Task Force and other recommendations to ensure its design was well suited to quantify the treatment preferences and trade-offs between the benefits and risks of treatments patients with HS are willing to accept(42-44). The survey was initially developed in English by a working group that included patient preference research experts and experienced dermatologists. An introductory section explained the survey and its content which included a description of the task prior to the presentation of the choice sets questions to participants. Prior to participation, respondents read a participant information sheet and provided consent online. The survey included questions to elicit participants' demographics, disease history and current health status. Participants' current health status was assessed using a pain visual-analogue scale (VAS), the EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L) and the Hidradenitis Suppurativa Quality of Life (HiSQOL) Questionnaire(45-47). The DCE experimental design was

split into three different, but equally sized blocks (or versions). Each of the three blocks contained 14 different choice questions based on an efficient design using Ngene software. One additional choice question included a dominance test; in which a dominant treatment option with no difference in mode of administration was presented to allow a later exclusion of participants who preferred the dominated option which indicated lack of understanding of the task(48,49). The survey was programmed and hosted online using Qualtrics® and participants were randomly assigned to one of the three blocks with 15 choice questions to avoid ordering effects. To respect the cognitive burden of the DCE on participants, the number of choice questions was limited to 15 and complemented by graphical illustrations. The survey was made available in English, Dutch or German with each translation verified by a native-speaking investigator. Participants were only allowed to progress in the survey if they had fully responded to all questions to avoid incomplete surveys. At the end of the survey, participants were asked to rate the difficulty of survey completion on a 0-10 scale (0=easy to 10=difficult).

5.3.4. Pilot-testing

The draft survey versions including the DCE questions were sequentially pilot-tested by five preference researchers, three dermatologists, and two patients with HS until finalisation. The attribute descriptions for the DCE survey were confirmed to be generally well understood, and the overall survey length was considered appropriate by the test persons, who felt that the hypothetical trade-offs were relevant, well-balanced, and not overly dominant. Only minor changes to the description of the survey and attributes were made following the pilot-testing.

5.3.5. Participants

Adult patients with confirmed diagnosis of HS in multiple European countries (Belgium, Germany, United Kingdom, Ireland, Switzerland, Austria, the Netherlands) were recruited through patient advocacy- and social media groups between January 2022 and April 2022. Optimal sample size for DCEs are challenging to predict as it depends on the true value of the parameters estimated in the DCE, which are not known prior to undertaking the research(44). Given the number of treatment options, attributes and levels included in the DCE, a minimum of 200 patients was targeted based on published guidance(50). Ethical approval for this study was obtained from the Medical Ethics Committee of the Academic Hospital Maastricht and Maastricht University. Additional local ethics approvals were obtained where required.

5.3.6. Statistical analyses

Participants' demographic and disease history variables including EQ-5D-5L and HiSQOL results were first checked for normality of variable and subsequently descriptively reported. The available patient preference data derived with the DCE was analysed using various recommended statistical methods and carried out using Nlogit software, version 5.0(51). First, the choice data from the DCE were analysed using a random-parameters logit (RPL) model which allows to capture heterogeneity by estimating the standard deviation of the parameter's distribution. Using an RPL model was consistent with good research practices, prior precedence for regulatory decision-making and provided mean coefficients as well as a measure of the distribution around the mean coefficient in the form of standard deviations(51). The conditional relative importance of each attribute was also calculated as the coefficient difference between the attribute level with the highest preference weight and the one with the lowest preference weight, to allow for comparisons across attributes. All variables were effects-coded; hence, the mean effect for each attribute was normalised at zero and the preference weights is relative to the mean effect of the different levels of the attribute. The model was estimated by using 1,000 Halton draws and no interaction terms were included in the final model, as an exploratory model with an interaction term provided similar fit and results. The sign of a coefficient reflects whether an attribute level led to an increase (positive) or a decrease (negative) on the participants' utility, while the value of each coefficient represents the importance participants assigned to each attribute level. P-values represent the statistical difference between the preference weight of the attribute levels and the mean effect of the same attribute; if the 95% confidence interval around two levels did not overlap, the differences between the preference weights were considered as statistically different(51). A-priori, it was expected that the attribute levels with large improvements such as high levels of effectiveness, pain reduction and duration of treatment benefit and lower risk of side-effects would have a positive effect on utility (i.e., a positive sign). Second, subgroup RPL models estimating the conditional relative importance were conducted to assess whether preferences varied as a function of patient characteristics or disease history. A range of subgroups covering country of residence, age, gender, disease severity, disease duration, current level of pain, HiSQOL score, previous biologic therapy and previous excisional surgery were considered based on the characteristics of the final sample. Binary subgroups for age, disease duration, current level of pain, and HiSQOL were created by dividing the sample by the median as conducted in previous preference research(52). Lastly, a latent class model was used to determine preference classes as they allow to identify the existence and number of classes in the population based on their treatment preferences(53). To determine the number of latent

classes, the model with the best fit based on the Akaike information criterion was selected from models with two, three, and four latent classes(51). The association between selected patient characteristics and latent class membership was then determined using a multivariable logistic regression model. The multivariable model was considered exploratory and was limited to the variables with different probability between latent classes. This analysis was conducted with IBM SPSS 24™.

5.4. Results

5.4.1. Study sample

A total of 224 participants completed the survey, of whom 219 were included in the analysis as five participants (<2.5%) did not pass the dominance test and were therefore excluded as pre-specified. The demographics of patients included in the DCE are reported in Table 5-2. Mean (standard deviation [SD]) age of participants was 38.7 (10.1) years and participants were predominantly female (90%) and of white/Caucasian ethnicity (94%). The HiSQOL median score (SD) of 34 (16.1) and pain median score (interquartile range) of 5 (3-7) indicate HS to have a large effect on patients' lives at time of questionnaire completion. The difficulty of questionnaire completion was reported on a 0–10 scale at 2.8 ± 2.7 (mean ± SD) by participants, which suggested that the survey completion was cognitively well manageable. Further demographics can be found in Table 5-2.

Table 5 - 2: Demographic characteristics of participants

Parameter		N=219	
Country, n (%)			
	United Kingdom	18	(8.2%)
	Ireland	22	(10.0%)
	Germany	71	(32.4%)
	Austria	3	(1.4%)
	Belgium	4	(1.8%)
	The Netherlands	68	(31.1%)
	Denmark	12	(5.5%)
	Switzerland	16	(7.3%)
	Other	5	(2.3%)
Gender, n (%)			
	Females	198	(90.4%)
Age (years), n (%)			
	≤30	49	(22.4%)
	31-40	78	(35.6%)
	41-50	64	(29.2%)
	>50	28	(12.8%)

Table 5 - 2: Continued.

Parameter		N=219	
Race, n (%)			
	White or Caucasian	205	(93.6%)
	Asian	3	(1.4%)
	Black or African American	0	-
	Other	11	(5.0%)
Occupational status, n (%)			
	Full-time employed	87	(39.7%)
	Part-time employed	51	(23.3%)
	Student	10	(4.6%)
	Not working or unemployed	31	(14.2%)
	Retired	40	(18.3%)
Highest level of education, n (%)			
	Primary or Elementary School	7	(3.2%)
	Secondary or High School	120	(54.8%)
	College or University Degree	73	(33.3%)
	Other	19	(8.7%)
Disease duration, (years), mean (SD)		10.70	(9.8)
Disease duration, n (%)			
	0-3	66	(30.1%)
	4-10	69	(31.5%)
	11-20	51	(23.3%)
	>20	33	(15.1%)
Severity of HS (by Hurley classification)			
	Mild	13	(5.9%)
	Moderate	132	(60.3%)
	Severe	74	(33.8%)
Treatment experience			
	Previous biologic therapy	65	(29.7%)
	Previous wide excisional surgery	134	(61.2%)
Level of pain (0-10 VAS), median (IQR)		5	3-7
HiSQOL score, median (SD)			
	Total score	34	(16.1)
	Symptom subscale	8	(4.1)
	Psychosocial subscale	10	(5.5)
	Activities and Adaptations subscale	17	(8.1)
EQ-5D-5L, mean (SD)			
	Mobility	2.14	(1)
	Self-care	1.50	(0.7)
	Usual Activities	2.21	(0.9)
	Pain & Discomfort	2.94	(1)
	Anxiety & Depression	2.58	(1.2)

Note: HS: hidradenitis suppurativa; SD: standard deviation; IQR: interquartile range; HiSQOL: Hidradenitis Suppurativa Quality of Life Questionnaire; EQ-5D-5L: EuroQoL 5-Dimension-5 Level Questionnaire; VAS: Visual Analogue Scale.

5.4.2. Participants' preferences

In all six treatment attributes, significant differences were observed between levels (as the 95% CI did not overlap), meaning that all attributes were important for participants as shown in Table 5-3. The most important treatment attribute for patients with HS was effectiveness (conditional relative importance of 47.9%) followed by pain reduction (17.3%), annual risk of mild AE (14.4%), annual risk of serious infection (10.3%), mode of administration (5.3%) and duration of treatment benefit (4.8%) as presented in Figure 5-2.

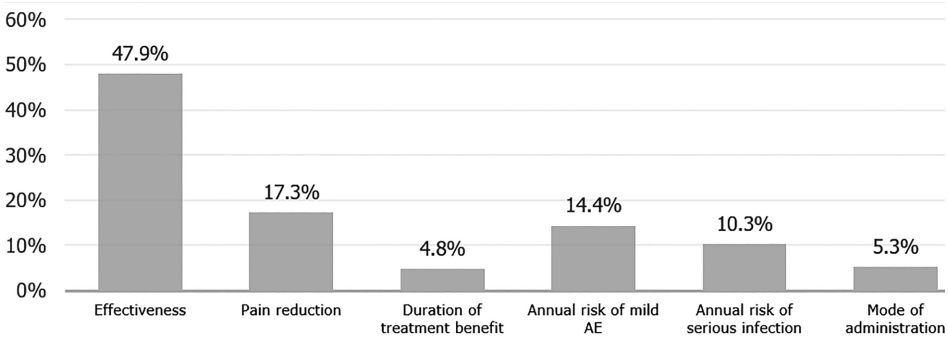


Figure 5 - 2: Conditional relative importance of treatment attributes
Note: AE: adverse event.

On average, respondents preferred treatment options with higher effectiveness, greater pain reduction, longer duration of treatment benefit, lower risk of mild AEs and serious infection which are offered as daily oral pill as can be observed from the random parameters logit model in Figure 5-3.

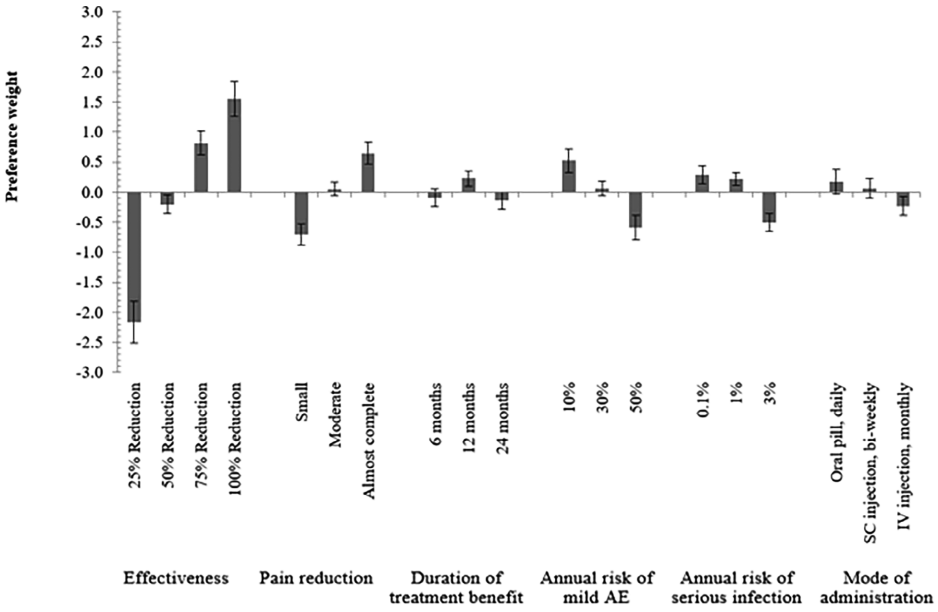


Figure 5 - 3: Random-parameters logit model estimates: preference weights (N=219).
Note: The vertical bars around each preference weight (coefficient estimate) represent the 95% confidence interval. Within each attribute, a higher preference weight indicates that a level is more preferred, and the sum of the preference weights equals 0. AE: adverse event; SC: subcutaneous; IV: intravenous.

The directions of relationships were observed as expected as the improved levels of each attribute resulted in higher coefficients values except for duration of treatment benefit for which participants preferred 12 months over 24 months (Table 5-3).

Table 5 - 3: Results from the random parameters logit model

Attribute	Level	Coefficient estimate (95% CI)[a]	p-value from previous level	Significant SD[b]
Effectiveness	25% Reduction	-2.165 (-2.519, -1.811)	-	-
	50% Reduction	-0.206 (-0.360, -0.052)	.009	No
	75% Reduction	0.818 (0.615, 1.020)	<.001	Yes
	100% Reduction	1.553 (1.258, 1.847)	<.001	Yes
Pain reduction	Small	-0.700 (-0.875, -0.525)	-	-
	Moderate	0.053 (-0.064, 0.170)	.369	No
	Almost complete	0.647 (0.465, 0.830)	<.001	Yes
Duration of treatment benefit	6 months	-0.092 (-0.240, 0.056)	-	-
	12 months	0.231 (0.103, 0.352)	<.001	No
	24 months	-0.139 (-0.279, 0.002)	.053	Yes
Annual risk of mild AE	10%	0.525 (0.331, 0.719)	-	-
	30%	0.064 (-0.055, 0.183)	.290	No
	50%	-0.589 (-0.797, -0.381)	<.001	Yes
Annual risk of serious infection	0.1%	0.288 (0.138, 0.439)	-	-
	1%	0.218 (0.105, 0.331)	<.001	No
	3%	-0.506 (-0.658, -0.354)	<.001	Yes
Mode of administration	Oral pill, daily	0.176 (-0.029, 0.381)	-	-
	SC injection, bi-weekly	0.057 (-0.107, 0.221)	.494	Yes
	IV injection, monthly	-0.233 (-0.390, -0.076)	<.001	Yes
K	26			
LL	-1,549.73			
AIC	3,151.5			

Note: [a]A positive (negative) sign for a given level indicates a level has a positive (negative) effect on utility. [b]Significance at 5%, standard deviations correspond to the random component of the model coefficients. AIC: Akaike information criterion; CI: confidence interval; K: number of parameters in the model; LL: log-likelihood; AE: adverse event; SC: subcutaneous; IV: intravenous; SD: standard deviation.

5.4.3. Subgroup analyses

The conditional relative importance of treatment attributes was generally consistent across subgroups (Figure 5-4). Patients with longer disease duration placed greater importance on treatment effectiveness and pain reduction rather than safety-related attributes compared to patients with shorter disease duration. Effectiveness and duration of treatment benefit were more important to patients with lower levels of pain while patients with higher levels preferred better pain

improvement. No subgroup analyses for gender, race/ethnicity and mild HS severity could be conducted due to sample size constraints.

5.4.4. Latent class model

The latent class analyses identified three preferences classes with class probabilities of 52%, 30% and 18% (Table 5-4), which indicates that patients value treatment characteristics differently. Effectiveness (60%), annual risk of mild AE (37%) and mode of administration (36%) were the most important attributes in each latent class, respectively. The preference coefficients of the latent class analyses are presented in the Appendix.

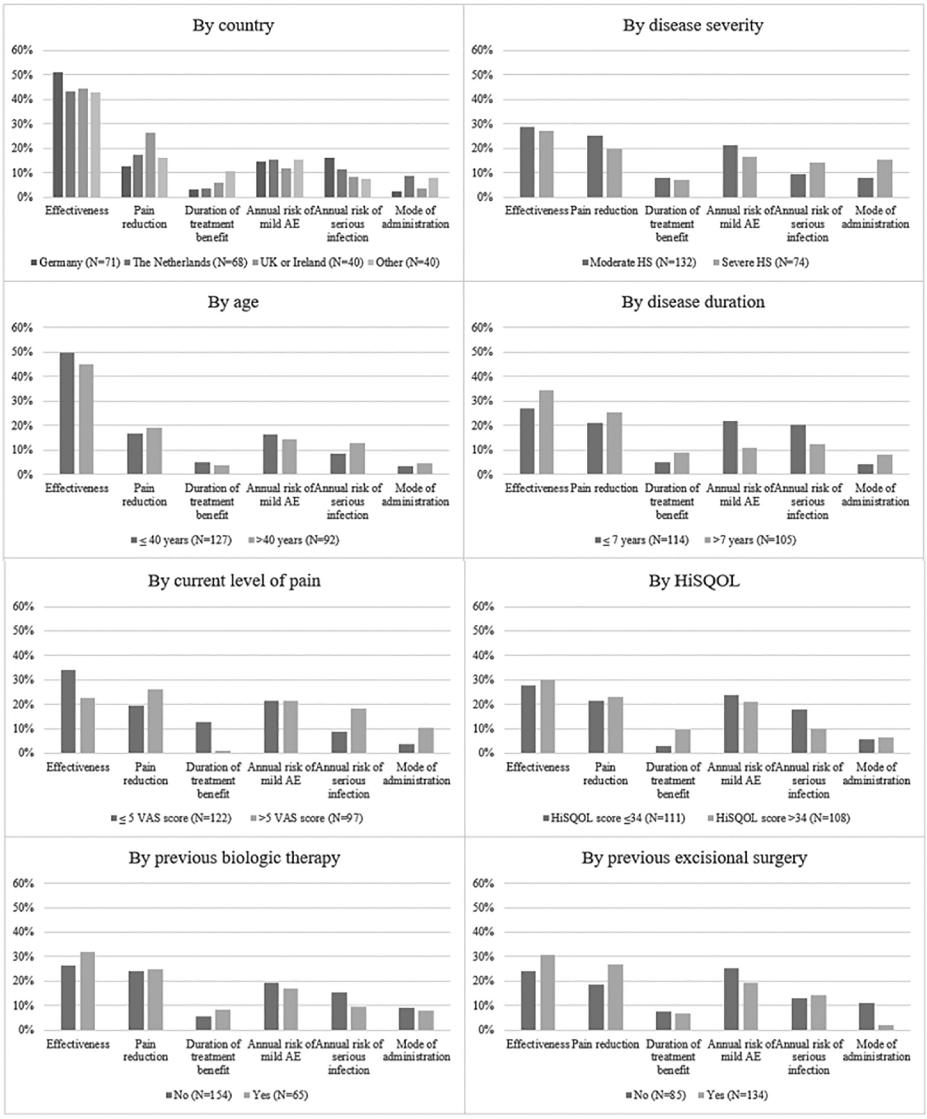


Figure 5 - 4: Conditional relative importance of treatment attributes for subgroups.
Note: Disease severity defined by Hurley classification. AE: adverse event; HiSQOL: Hidradenitis Suppurativa Quality of Life Questionnaire; VAS: visual analogue scale; HS: hidradenitis suppurativa.

Table 5 - 4: Latent class analyses: Latent class probabilities and conditional relative importance between attributes

Treatment Attribute	Overall	Latent class 1 (52%)	Latent class 2 (30%)	Latent class 3 (18%)
Effectiveness	48%	60%	25%	11%
Pain reduction	17%	14%	17%	21%
Duration of treatment benefit	5%	7%	4%	6%
Annual risk of mild AE	15%	4%	37%	7%
Annual risk of serious infection	10%	8%	11%	19%
Mode of administration	5%	7%	6%	36%

Note: Akaike information criterion= 3313.8. AE: adverse event.

5.5. Discussion

This study aimed to reveal which treatment attributes adult patients with HS consider most important when making treatment decisions. It reported numerous novel findings by quantifying treatment attribute preferences of patients with HS in Europe using a DCE. All six selected treatment attributes (effectiveness, pain reduction, duration of treatment benefit, annual risk of mild AE, annual risk of serious infection and mode of administration) were important for HS patients and consistent with a-priori expectations in terms of the direction and magnitude of the estimated coefficients. 'Effectiveness' was the most important treatment attribute for patients, which confirmed the previously reported high unmet needs regarding treatment outcomes as only one-third of patients experience remission of their disease over time with currently available treatment options(7,11,12,21). Interestingly, while previous clinical trials of HS treatments primarily investigated a 50% reduction of abscess and inflammatory nodule (AN) count, patients in this research considered more stringent measures of treatment effectiveness, such as 75% and 100% levels of reduction of AN count to be more relevant(16,31). This likely reflects increasing expectations regarding treatment success in people with HS which demonstrates that future HS clinical trials may need to consider a higher efficacy target to demonstrate treatment effectiveness. The results further highlighted the significance for patients to experience better pain control as it was the second most important treatment attribute and was also determined as relevant by the HISTORIC core outcomes set initiative and previous research(21,54). Patients generally preferred 12 months duration of treatment benefit over 6 months but did not prefer the benefits to last 24 months, which may indicate patients' reluctance

to commit to a therapy administered as injection or oral pill beyond one year. The least preferred mode of administration was the monthly IV injection, which is aligned to the conclusions of a recent literature review in chronic immune system disorders that patients preferred treatment at home due to the convenience and comfort of home treatment and the avoidance of having to attend hospital for IV injection albeit less frequently administered(55). Extensive subgroup analyses confirmed that observed differences in preferences were not explained by patient characteristics or disease history as participants' treatment preferences were generally consistent across subgroups. Some variations in preferences were observed in patients with longer disease duration and higher levels of pain, both placing more importance on treatment effectiveness and pain reduction and duration of treatment benefit, respectively. The latent class analyses identified three distinct groups of respondents whose most important treatment attributes were effectiveness, annual risk of mild AE and mode of administration, revealing heterogeneity in preferences between patients. The findings of this study highlight the importance of investigating individual preferences and incorporating them not only in clinical decision-making but also in research-, regulatory-, and policy decisions. Treatments for patients with HS should offer higher levels of effectiveness than are typically reported as primary outcomes in current clinical trials, result in greater pain improvement, and minimise the risk of adverse events when possible. Treatments administered as IV injection are generally the least desirable mode of administration. One latent class strongly favored oral treatments, but for most patients, efficacy was the most important factor determining treatment preference. Ultimately, a variety of treatment options should be made available so that treatment can be individualised based on patient preference. Although this study followed good research practices, was designed with experienced HCPs and preference research experts, and underwent extensive pilot-testing, some limitations are to be considered in the interpretation of the results. While most participants' demographics are in line with recent research and were overall well-balanced, no Black- or African American patients participated in this study and most patients reported moderate or severe HS, with only few patients having mild HS(13). In addition, the sample size was targeted for the whole sample which impaired ability to confirm findings for every country individually. Although extensive qualitative research with patients and HCPs was conducted to select and define attributes and levels for this DCE, additional or different attributes or levels could have led to varying findings(21). For example, costs could be an important attribute to be added in future DCEs in countries where patients have considerable out-of-pocket cost contributions, which was assessed not to be the case in the countries included in this research(56). Finally, despite DCEs being widely used, they have the inherent limitation that respondents are

stating their preferences on hypothetical treatments, which may differ from their preferences in real-life treatment decision-making(57). Future research can further advance the understanding of treatment preferences in HS by conducting DCEs with patients in other geographies or with HCPs to allow comparisons of findings between participant groups or explore the impact of different attributes and levels on patient's stated preferences.

5.6. Conclusions

This research highlighted the patient perspectives surrounding the relevant benefits and risks of different HS treatments, which can help clinical-, regulatory, reimbursement, and development decision-making to allow future HS treatment to become better suited to patients' needs and preferences and ultimately lead to improved disease management. It was revealed HS patients preferred treatments offering higher levels of effectiveness and pain reduction.

5.7. References

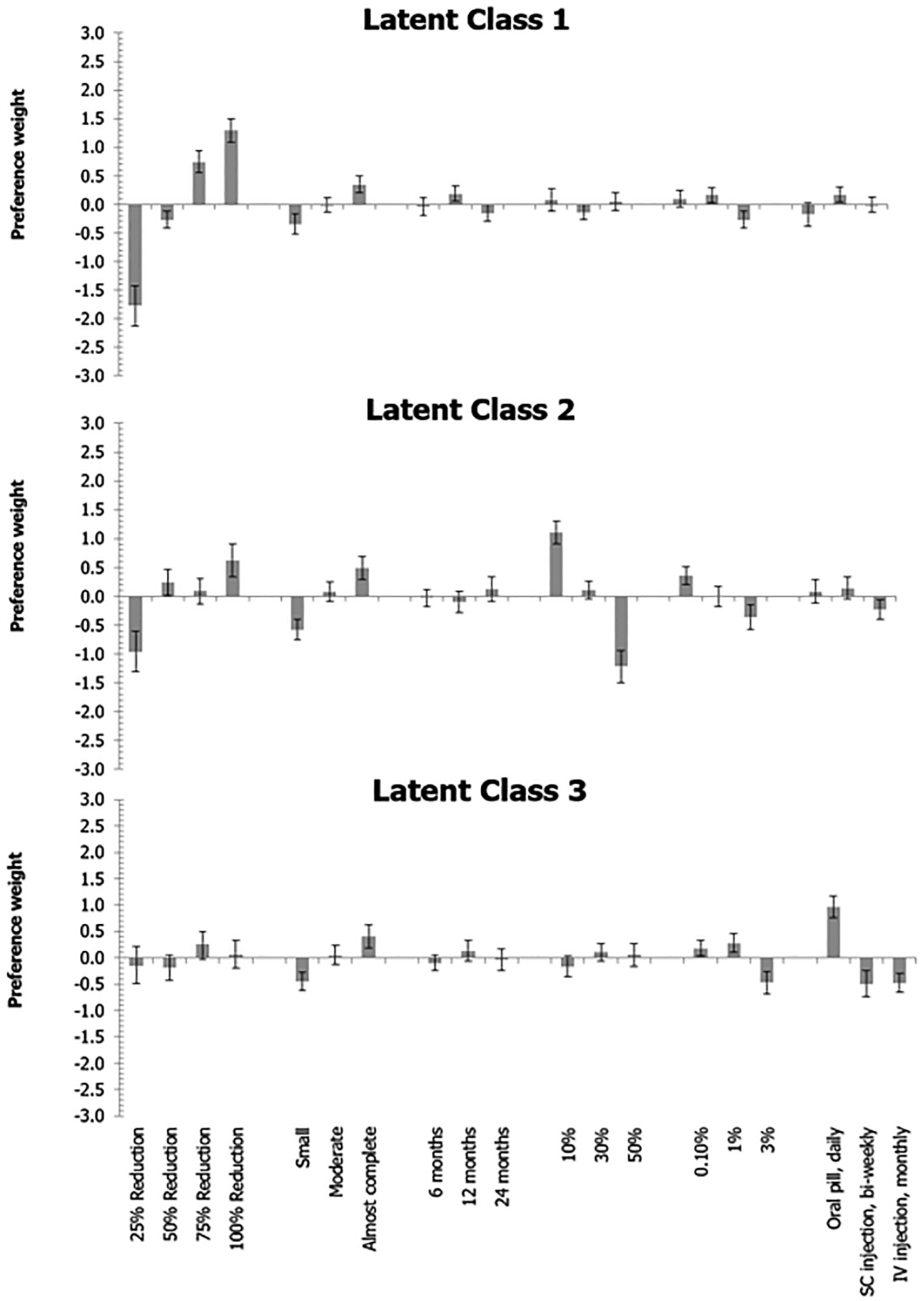
1. Montero-Vilchez T, Diaz-Calvillo P, Rodriguez-Pozo JA et al. The Burden of Hidradenitis Suppurativa Signs and Symptoms in Quality of Life: Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2021;18.
2. Fisher S, Ziv M. Interviewing Women with Hidradenitis Suppurativa-Thematic and Content Analysis. Adv Skin Wound Care 2022;35:381-384.
3. Jemec GB. Clinical practice. Hidradenitis suppurativa. N Engl J Med 2012;366:158-64.
4. Kirsten N, Petersen J, Hagenstrom K, Augustin M. Epidemiology of hidradenitis suppurativa in Germany - an observational cohort study based on a multisource approach. J Eur Acad Dermatol Venereol 2020;34:174-179.
5. Kokolakis G, Wolk K, Schneider-Burrus S et al. Delayed Diagnosis of Hidradenitis Suppurativa and Its Effect on Patients and Healthcare System. Dermatology 2020;236:421-430.
6. Saunte DM, Boer J, Stratigos A et al. Diagnostic delay in hidradenitis suppurativa is a global problem. Br J Dermatol 2015;173:1546-9.
7. 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;82:366-376.
8. Zouboulis CC, Del Marmol V, Mrowietz U, Prens EP, Tzellos T, Jemec GB. Hidradenitis Suppurativa/Acne Inversa: Criteria for Diagnosis, Severity Assessment, Classification and Disease Evaluation. Dermatology 2015;231:184-90.
9. 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.
10. Aarts P, Dudink K, Vossen A et al. Clinical Implementation of Biologics and Small Molecules in the Treatment of Hidradenitis Suppurativa. Drugs 2021;81:1397-1410.
11. Ingram JR, Bettoli V, Espy JI et al. Unmet clinical needs and burden of disease in hidradenitis suppurativa: real-world experience from EU5 and US. J Eur Acad Dermatol Venereol 2022.
12. Kjaersgaard Andersen R, Loft IC, Hansen T et al. Incidence and remission rates of self-reported hidradenitis suppurativa - A prospective cohort study conducted in Danish blood donors. J Eur Acad Dermatol Venereol 2022;36:717-725.
13. De DR, Shih T, Fixsen D, Brooks B, Hsiao JL, Shi VY. Biologic Use in Hidradenitis Suppurativa: Patient Perspectives and Barriers. J Dermatolog Treat 2022:1-4.
14. Markota Cagalj A, Marinovic B, Bukvic Mokos Z. New and Emerging Targeted Therapies for Hidradenitis Suppurativa. Int J Mol Sci 2022;23.
15. Huang CH, Huang IH, Tai CC, Chi CC. Biologics and Small Molecule Inhibitors for Treating Hidradenitis Suppurativa: A Systematic Review and Meta-Analysis. Biomedicines 2022;10.
16. Glatt S, Jemec GBE, Forman S et al. Efficacy and Safety of Bimekizumab in Moderate to Severe Hidradenitis Suppurativa: A Phase 2, Double-blind, Placebo-Controlled Randomized Clinical Trial. JAMA Dermatol 2021;157:1279-1288.
17. Zouboulis CC, Frew JW, Giamarellos-Bourboulis EJ et al. Target molecules for future hidradenitis suppurativa treatment. Exp Dermatol 2021;30 Suppl 1:8-17.

18. Kimball A. Secukinumab in Moderate-to-Severe Hidradenitis Suppurativa: Primary Endpoint Analysis from the SUNSHINE and SUNRISE Phase III Trials. Proceedings of the 31st European Academy of Dermatology and Venereology (EADV) Congress, Milan, Italy, 2022:7-10.
19. Dermatology-Times. UCB Announces Positive Phase 3 Studies for Bimekizumab in Hidradenitis Suppurativa. In: Nagorka C, editor, 2022.
20. Umar N, Schaarschmidt M, Schmieder A, Peitsch WK, Schollgen I, Terris DD. Matching physicians' treatment recommendations to patients' treatment preferences is associated with improvement in treatment satisfaction. J Eur Acad Dermatol Venereol 2013;27:763-70.
21. Willems D, Hiligsmann M, van der Zee HH, Sayed CJ, Evers S. Identifying Unmet Care Needs and Important Treatment Attributes in the Management of Hidradenitis Suppurativa: A Qualitative Interview Study. Patient 2022;15:207-218.
22. Bouvy JC, Cowie L, Lovett R, Morrison D, Livingstone H, Crabb N. Use of Patient Preference Studies in HTA Decision Making: A NICE Perspective. Patient 2020;13:145-149.
23. Ho MP, Gonzalez JM, Lerner HP et al. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc 2015;29:2984-93.
24. Willems D, Charokopou M, Evers S, Hiligsmann M. Early health economic modelling for a treatment candidate in hidradenitis suppurativa. J Med Econ 2020;23:1516-1524.
25. Jevtic T, Bukumiric Z, Jankovic SM. Effects of treatment adherence on clinical and economic outcomes in patients with psoriasis. Med Glas (Zenica) 2013;10:106-12.
26. Sain N, Willems D, Charokopou M, Hiligsmann M. The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments. Curr Med Res Opin 2020;36:1257-1275.
27. Gaspar K, Hunor Gergely L, Jenei B et al. Resource utilization, work productivity and costs in patients with hidradenitis suppurativa: a cost-of-illness study. Expert Rev Pharmacoecon Outcomes Res 2021:1-10.
28. Schaarschmidt ML, Umar N, Schmieder A et al. Patient preferences for psoriasis treatments: impact of treatment experience. J Eur Acad Dermatol Venereol 2013;27:187-98.
29. Thorneloe RJ, Bundy C, Griffiths CE, Ashcroft DM, Cordingley L. Nonadherence to psoriasis medication as an outcome of limited coping resources and conflicting goals: findings from a qualitative interview study with people with psoriasis. Br J Dermatol 2017;176:667-676.
30. Vass C, Rigby D, Payne K. The Role of Qualitative Research Methods in Discrete Choice Experiments. Med Decis Making 2017;37:298-313.
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. Muhlbacher AC, Junker U, Juhnke C et al. Chronic pain patients' treatment preferences: a discrete-choice experiment. Eur J Health Econ 2015;16:613-28.
33. Sumpton D, Kelly A, Craig JC et al. Preferences for Biologic Treatment in Patients With Psoriatic Arthritis: A Discrete Choice Experiment. Arthritis Care Res (Hoboken) 2021.
34. 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;85:369-378.

35. Jensen MP, Chen C, Brugger AM. Interpretation of visual analog scale ratings and change scores: a reanalysis of two clinical trials of postoperative pain. J Pain 2003;4:407-14.
36. Copsey B, Buchanan J, Fitzpatrick R, Lamb SE, Dutton SJ, Cook JA. Duration of Treatment Effect Should Be Considered in the Design and Interpretation of Clinical Trials: Results of a Discrete Choice Experiment. Med Decis Making 2019;39:461-473.
37. Zouboulis CC, Okun MM, Prens EP et al. Long-term adalimumab efficacy in patients with moderate-to-severe hidradenitis suppurativa/acne inversa: 3-year results of a phase 3 open-label extension study. J Am Acad Dermatol 2019;80:60-69 e2.
38. Prens LM, Bouwman K, Aarts P et al. Adalimumab and infliximab survival in patients with hidradenitis suppurativa: a daily practice cohort study. Br J Dermatol 2021;185:177-184.
39. Quartuccio L, Zabotti A, Del Zotto S, Zanier L, De Vita S, Valent F. Risk of serious infection among patients receiving biologics for chronic inflammatory diseases: Usefulness of administrative data. J Adv Res 2019;15:87-93.
40. Dixon WG, Watson K, Lunt M et al. Rates of serious infection, including site-specific and bacterial intracellular infection, in rheumatoid arthritis patients receiving anti-tumor necrosis factor therapy: results from the British Society for Rheumatology Biologics Register. Arthritis Rheum 2006;54:2368-76.
41. Ghias MH, Johnston AD, Kutner AJ, Micheletti RG, Hosgood HD, Cohen SR. High-dose, high-frequency infliximab: A novel treatment paradigm for hidradenitis suppurativa. J Am Acad Dermatol 2020;82:1094-1101.
42. Bridges JF, Hauber AB, Marshall D et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health 2011;14:403-13.
43. Reed Johnson F, Lancsar E, Marshall D et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health 2013;16:3-13.
44. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics 2008;26:661-77.
45. 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;183:340-348.
46. Riis PT, Vinding GR, Ring HC, Jemec GB. Disutility in Patients with Hidradenitis Suppurativa: A Cross-sectional Study Using EuroQoL-5D. Acta Derm Venereol 2016;96:222-6.
47. Bato A, Brodszky V, Gergely LH et al. The measurement performance of the EQ-5D-5L versus EQ-5D-3L in patients with hidradenitis suppurativa. Qual Life Res 2021;30:1477-1490.
48. Tervonen T, Schmidt-Ott T, Marsh K, Bridges JFP, Quaife M, Janssen E. Assessing Rationality in Discrete Choice Experiments in Health: An Investigation into the Use of Dominance Tests. Value Health 2018;21:1192-1197.
49. Janssen EM, Marshall DA, Hauber AB, Bridges JFP. Improving the quality of discrete-choice experiments in health: how can we assess validity and reliability? Expert Rev Pharmacoecon Outcomes Res 2017;17:531-542.

50. de Bekker-Grob EW, Donkers B, Jonker MF, Stolk EA. Sample Size Requirements for Discrete-Choice Experiments in Healthcare: a Practical Guide. Patient 2015;8:373-84.
51. Hauber AB, Gonzalez JM, Groothuis-Oudshoorn CG et al. Statistical Methods for the Analysis of Discrete Choice Experiments: A Report of the ISPOR Conjoint Analysis Good Research Practices Task Force. Value Health 2016;19:300-15.
52. Boeri M, Sutphin J, Hauber B, Cappelleri JC, Romero W, Di Bonaventura M. Quantifying patient preferences for systemic atopic dermatitis treatments using a discrete-choice experiment. J Dermatolog Treat 2020:1-10.
53. Zhou M, Thayer WM, Bridges JFP. Using Latent Class Analysis to Model Preference Heterogeneity in Health: A Systematic Review. Pharmacoeconomics 2018;36:175-187.
54. 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;179:642-650.
55. Overton PM, Shalet N, Somers F, Allen JA. Patient Preferences for Subcutaneous versus Intravenous Administration of Treatment for Chronic Immune System Disorders: A Systematic Review. Patient Prefer Adherence 2021;15:811-834.
56. Somers C, Chimonas S, McIntosh E, Kaltenboeck A, Briggs A, Bach P. Using Nominal Group Technique to Identify Key Attributes of Oncology Treatments for a Discrete Choice Experiment. MDM Policy Pract 2019;4:2381468319837925.
57. Laba TL, Brien JA, Fransen M, Jan S. Patient preferences for adherence to treatment for osteoarthritis: the MEdication Decisions in Osteoarthritis Study (MEDOS). BMC Musculoskelet Disord 2013;14:160.

Appendix 5.8.



Appendix Figure 5 - 1: Random-parameters logit model estimates of latent classes.
Note: The vertical bars around each preference coefficient represent the 95% confidence interval. Within each attribute, a higher preference coefficient indicates that a level is more preferred, and the sum of the preference coefficient equals 0. AE: adverse event; SC: subcutaneous; IV: intravenous.

6

A discrete-choice experiment to elicit the treatment preferences of patients with hidradenitis suppurativa in the United States

Chapter 6 was informed by:
Willems, D., Sayed, C. J., Van der Zee, H. H., Ingram, J. R., Hinzpeter, E., Beaudart, C., Evers, S., & Hiligsmann, M. (2023). A discrete-choice experiment to elicit the treatment preferences of patients with hidradenitis suppurativa in the United States. *Journal of Medical Economics*, 26(1), 503-508.

6.1. Introduction

Hidradenitis suppurativa (HS), is a chronic inflammatory skin disease characterized by recurrent nodules, tunnels, and scarring in flexural skin locations that may lead to a severe reduction in quality of life(1). The prevalence of HS in the US is reported between 0.03–1% with onset at an average age of 22 years and a diagnostic delay between 7 and 10 years(2). For mild patients with HS, antibacterial treatments are recommended, and anti-inflammatory treatments are frequently used for moderate HS. Surgery is typically used to address recurrent lesions, symptomatic scars, and chronically inflamed tunnels(3). Adalimumab is the only Food and Drug Administration-approved biologic therapy currently available in the US for patients with moderate-to-severe HS, with approximately half of the patients failing to achieve a meaningful clinical response(3-5). With the expected introduction of novel treatment options such as bimekizumab and secukinumab which recently reported positive phase III results to address this heterogeneous disease, the importance of understanding patients' preferences in treatment decision-making is critical(6-8). Preference research is becoming increasingly important in regulatory- and reimbursement decision-making, while accounting for preferences in clinical practice could improve shared decision-making and positively influence treatment outcomes, satisfaction, and adherence which in turn could reduce the high humanistic and socio-economic burden of HS(9-11). A discrete-choice experiment (DCE) was recently conducted with HS patients in Europe but the transferability of these preference findings to other geographies is uncertain due to potential differences in care pathways(12). At the time of this research, no DCE was yet conducted with HS patients in the US. Therefore, the aims of this study were to conduct a DCE with HS patients in the US that was similar to a recent DCE done with European patients to reveal treatment preferences of US patients and to compare their characteristics and preferences with patients in Europe(12).

6.2. Materials and methods

In this study, the same DCE questionnaire was used that elicited the treatment preferences of HS patients in Europe(12). In the DCE questionnaire, participants were first asked about their demographics, socioeconomic characteristics and current health status using a pain visual-analogue scale (VAS), the EuroQoL 5-Dimension 5-Level Questionnaire (EQ-5D-5L) and the Hidradenitis Suppurativa Quality of Life (HiSQOL) before being asked to repetitively choose between one of two hypothetical treatments(13). The two hypothetical treatments differed in terms of [a] effectiveness on reducing the number of painful, inflammatory

lesions, [b] reduction of pain, [c] duration of treatment benefit, [d] risk of mild side effects, [e] risk of serious infection and [f] mode of administration. Detailed information on the methodology of attribute and level selection was previously reported(12). In short, a literature review and qualitative interviews with patients and clinicians were conducted to identify the most relevant attributes and levels for the DCE(12,14). The draft questionnaire was sequentially pilot-tested by five preference researchers, three dermatologists, and two patients. Adult patients with HS in the US were invited through patient advocacy and social media groups between August 2022 and December 2022 to complete the online questionnaire hosted in Qualtrics®. Participants were only allowed to proceed in the survey if the location 'United States' was selected and if the informed consent was provided online. After completing the socio-demographics questions, each participant was randomly assigned to one of three DCE blocks (designed in Ngene using an efficient experimental design to avoid ordering effects), each containing the identical 15 choice sets as previously used(12). One choice set included a dominance test in which one hypothetical treatment had clearly better outcomes than the other, to assess the reliability of patients' choices. Patients who failed the dominance test were excluded from the analyses. At the end of the questionnaire, participants were asked to rate the difficulty of completion on a 0-10 scale (0=easy to 10=difficult). Ethical approval for this study was obtained from the Medical Ethics Committee of the Academic Hospital Maastricht and Maastricht University. Analyses of the patient preference data were carried out using Nlogit software, version 5.0 and followed a similar approach as previously described(12). Briefly, a random parameter logit (RPL) model was used to derive the mean coefficients and the distribution around them using standard deviations (SD). The conditional relative importance of the attributes was derived from the difference between the attribute level with the highest coefficient estimate and the one with the lowest. The coefficient indicated whether an attribute level led to an increase (positive) or a decrease (negative) of the participants' utility. *P-values* characterized the statistical difference between the coefficient of the attribute levels and the mean effect of the attribute; if the 95% confidence interval (CI) around two levels did not overlap, the differences were considered as statistically different. Non-overlapping SDs with zero indicate significant heterogeneity among patients' preferences for a given attribute level. Subgroup analyses were not conducted due to sample size constraints, but a statistical comparison of the characteristics of patients with HS in the US and Europe was conducted using t-tests for continuous variables and chi-square tests for categorical variables in IMB SPPS Statistics 21.0. Descriptive statistics were used for the comparisons of conditional relative importance results between patients with HS in the US and Europe.

6.3. Results

A total of 100 patients with HS in the US completed the questionnaire, of whom 99 were included in the analysis as one patient (1%) did not pass the dominance test and was excluded from analyses as pre-specified. The demographics of patients included in the DCE are reported in Table 6-1. Mean age (SD) of participants was 41.7 (12.0) years and participants were predominantly female (90%) and of white/ Caucasian ethnicity (69%). The HiSQOL median score (SD) of 36.9 (15.7) and pain median score (interquartile range) of 4.9 (2.5-7.0) indicated HS to have a profound effect on patients' quality of life at time of questionnaire completion. The difficulty to complete the questionnaire was stated on a 0–10 scale at 2.4 ± 2.4 (mean ± SD) by participants, which suggested a cognitively intuitive questionnaire.

Table 6 - 1: Demographic characteristics of participants

Parameter		N=99	
Gender, n (%)			
	Females	90	(90.9%)
Age (years), mean (SD)		41.7	(12.0)
Race, n (%)			
	White or Caucasian	69	(69.7%)
	Black or African American	18	(18.2%)
	Asian	1	(1.0%)
	Hispanic or Latino	7	(7.1%)
	Other	4	(4.0%)
Occupational status, n (%)			
	Full-time employed	54	(54.5%)
	Part-time employed	5	(5.1%)
	Self-employed	2	(2.0%)
	Student	5	(5.1%)
	Not working or unemployed	23	(23.2%)
	Retired	10	(10.1%)
Highest level of education, n (%)			
	Primary or Elementary School	2	(2.0%)
	Secondary or High School	35	(35.4%)
	College or University Degree	54	(54.5%)
	Other	8	(8.1%)
Type of health insurance			
	Private	59	(59.6%)
	Public	33	(33.3%)
	Not insured	7	(7.1%)

Table 6 - 1: Continued.

Parameter	N=99	
Disease duration, (years), mean (SD)	10.8	(9.53)
Severity of HS		
Mild	11	(11.1%)
Moderate	47	(47.5%)
Severe	41	(41.4%)
Treatment experience		
Previous biologic therapy	47	(47.5%)
Previous wide excisional surgery	44	(44.4%)
Level of pain (0-10 VAS), median (IQR)	5	2.5-7
HiSQOL score, median (SD)		
Total score	37	(15.71)
Symptom subscale	9	(4.12)
Psychosocial subscale	12	(5.29)
Activities and Adaptations subscale	17	(7.74)
EQ-5D-5L, mean (SD)		
Mobility	2.18	(0.81)
Self-care	2.07	(1.01)
Usual Activities	2.48	(1.04)
Pain & Discomfort	2.89	(0.77)
Anxiety & Depression	2.00	(0.97)

Note: HS: hidradenitis suppurativa; SD: standard deviation; IQR: interquartile range; HiSQOL: Hidradenitis Suppurativa Quality of Life Questionnaire; EQ-5D-5L: EuroQoL 5-Dimension-5 Level Questionnaire; VAS: Visual Analogue Scale.

The most important treatment attribute for patients in the US was effectiveness (conditional relative importance of 56.3%) followed by pain reduction (16.0%), annual risk of mild AE (9.4%), mode of administration (8.3%), duration of treatment benefit (5.9%), and annual risk of serious infection (4.0%) as presented in Table 6-2. In all treatment attributes, except annual risk of serious infection, significant differences were observed between levels (as the 95% CI did not overlap), suggesting that effectiveness, pain reduction, duration of treatment benefit, annual risk of mild AE, and mode of administration were important to patients. On average, patients in the US preferred treatment options offering higher effectiveness, greater pain reduction, lower annual risk of mild AEs and serious infection which are either administered as daily oral pill or bi-weekly subcutaneous injection as shown in the RPL model in Figure 6-1.

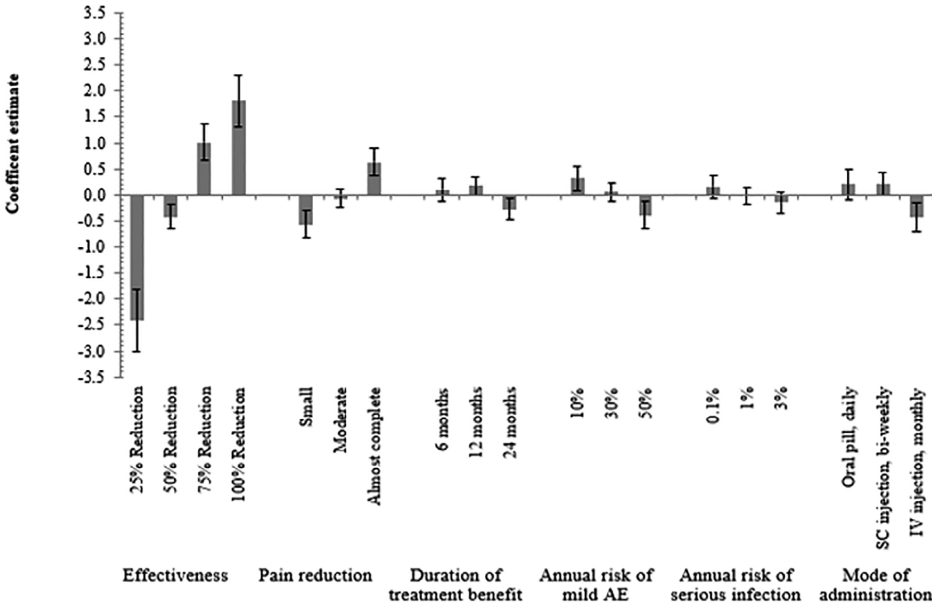


Figure 6 - 1: Random-parameters logit model estimates: coefficient estimate (N=99).
Note: The vertical bars around each coefficient estimate (preference weight) represent the 95% confidence interval. Within each attribute, a higher coefficient estimate indicates a level being more preferred, and the sum of the coefficient estimates equals 0. AE: adverse event; SC: subcutaneous; IV: intravenous.

The directions of relationships were observed as expected with improved levels of each attribute resulting in higher coefficient values except for duration of treatment benefit for which participants least preferred the 24 months duration (Table 6-2). The demographic characteristics of patients with HS in the US were significantly different from patients in Europe with regards to age (41.7 vs. 38.7 years; p=0.024), ethnicity (p<0.001), previous biologic treatment (47.5% vs. 29.7%; p=0.002), previous wide excisional surgery (44.4% vs. 61.2%; p=0.005) and HiSQOL (36.9 vs. 32.9 mean total score; p=0.04). The observed differences in gender (90.9% vs 90.4% females), time since diagnosis (10.8 vs 10.9 years), disease severity (11.1% vs. 5.9% mild HS; 47.5% vs. 60.3% moderate HS; 41.4% vs. 33.8% severe HS), level of pain (4.92 vs. 4.74 median) and EQ-5D-5L (2.34 vs. 2.27 mean total score) were non-significant (p>0.05)(12).

Table 6 - 2: Results from the random parameters logit model of the DCE with US patients

Attribute (relative importance)	Level	Coefficient estimate (95% CI)[a]	p-value	Significant SD[b]
Effectiveness (56.3%)	25% Reduction	-2.405 (-3.009, -1.800)	-	-
	50% Reduction	-0.416 (-0.661, -0.172)	<.001	No
	75% Reduction	1.011 (0.661, 1.362)	<.001	Yes
	100% Reduction	1. 809 (1.319, 2.300)	<.001	Yes
Pain reduction (16.0%)	Small	-0.565 (-0.822, -0.307)	-	-
	Moderate	-0.070 (-0.248, 0.108)	.442	No
	Almost complete	0.634 (0.370, 0.899)	<.001	Yes
Duration of treatment benefit (5.9%)	6 months	0.100 (-0.121, 0.320)	-	-
	12 months	0.172 (-0.015, 0.360)	.072	No
	24 months	-0.272 (-0.486, -0.059)	.124	Yes
Annual risk of mild AE (9.4%)	10%	0.322 (0.083, 0.562)	-	-
	30%	0.062 (-0.116, 0.240)	.494	No
	50%	-0.384 (-0.640, -0.129)	.003	Yes
Annual risk of serious infection (4.0%)	0.1%	0.157 (0.138, 0.439)	-	-
	1%	-0.013 (-0.174, 0.148)	.876	No
	3%	-0.144 (-0.347, -0.059)	.165	Yes
Mode of administration (8.3%)	Oral pill, daily	0.208 (-0.079, 0.495)	-	-
	SC injection, bi-weekly	0.209 (-0.007, 0.424)	.058	Yes
	IV injection, monthly	-0.417 (-0.691, -0.142)	.003	Yes
K	26			
LL	-682.37			
AIC	1416.7			

Note: [a]A positive (negative) sign for a given level indicates a level has a positive (negative) effect on utility. [b]Significance at 5%, standard deviations correspond to the random component of the model coefficients. AIC: Akaike information criterion; CI: confidence interval; K: number of parameters in the model; LL: log-likelihood; AE: adverse event; SC: subcutaneous; IV: intravenous; SD: standard deviation.

Considering the comparison of treatment preferences, patients in the US and Europe both stated effectiveness and pain reduction to be the two most important treatment attributes, with conditional relative importance of 56.3% and 47.9%, and 16.0% and 17.3%, respectively as shown in Figure 6-2. Patients in the US placed greater importance than patients in Europe on mode of administration (8.3% vs. 5.3%) and less importance on annual risk of mild AE (9.4% vs 14.4%) and serious infection (4.0% vs 10.3%)(12). Monthly IV injection was the least preferred mode of administration for patients in US and Europe(12).

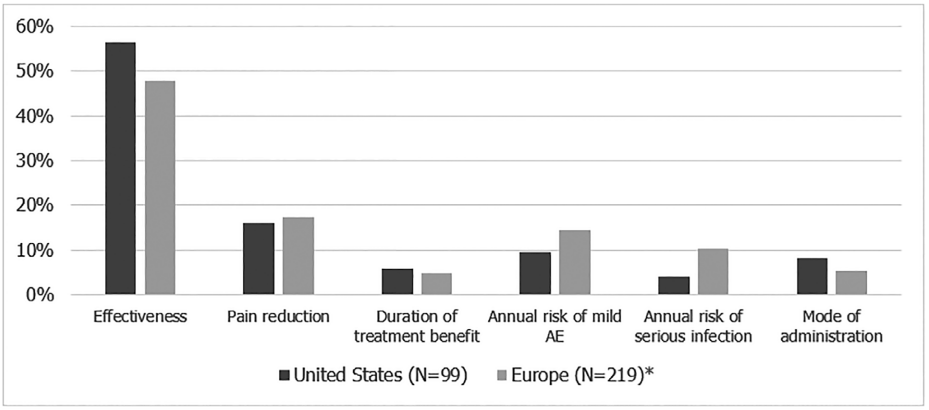


Figure 6 - 2: Comparison of conditional relative importance of treatment attributes between US and European patients.
*Note: AE: adverse event. *Adapted from Willems et al. (2023)(12).*

6.4. Discussion

This study revealed the treatment attributes patients with HS in the US valued the most in therapy decision-making. Effectiveness, pain reduction, annual risk of mild AE and mode of administration were most relevant to patients when deciding between two hypothetical treatment options. Effectiveness was the most important treatment attribute, which could be attributable to the high unmet needs reported by patients due to low treatment success and satisfaction with current available therapies for HS(4,5,14). Higher levels of effectiveness aiming at a 75% and 100% reduction of abscess and nodule count, which represent more stringent effectiveness targets than the primary endpoint of most clinical trials in HS, were more important to patients(15). Pain reduction being the second most important treatment attribute confirmed the findings of previous research that pain management is often not successful or overlooked in the management of HS(12,14,16). Patients preferred treatments with a duration of benefit of 6 and 12 months over 24 months, which may seem counter-intuitive but is in line with previous research reporting low willingness by patients to commit to a treatment beyond one year(17). Treatments offered as monthly IV injection were least preferred, likely attributable to the associated inconvenience for patients having to attend a clinic for IV injection compared to the comfort of treatment at home as previously concluded(18). The statistical comparison of sample characteristics between patients in the US and Europe revealed the patients to be comparable in terms of gender, time since diagnosis, disease duration, current level pain, and

EQ-5D-5L scores(12). The statistically significant differences observed for age, ethnicity, biologic treatment experience, wide excisional surgery experience, and HiSQOL scores did not lead to strong variations in stated preferences between US and European patients as both groups considered effectiveness and pain reduction most important. The only considerable difference observed was US patients placing greater importance on the mode of administration than patients in Europe(12). These findings are also similar to another recently conducted DCE in Germany which also revealed therapeutic success to be the most important treatment attribute for patients with HS (N=216), and safety attributes also to be the least important attributes in treatment decision-making(19). The preferred mode of administration was oral tablets followed by subcutaneous injection, which is in line with results of this study(19). This research adhered to high preference research standards, but nevertheless has some limitations to be considered in the interpretation of the results. While most participants' demographics were well-balanced and generally similar to recent preference research in other geographies, the ethnic variation of the sample may hinder the generalizability of findings(12,14,19). The sample size further impaired subgroup analyses, but the sample characteristics and preference results were compared in detail with similar research in Europe(12,19). Despite having developed the questionnaire with patients and clinicians (of which 3 were located in the US), and selecting the attributes and levels in accordance with best research practices, different attributes or levels could have led to varying preference results as recently revealed by Faverio et al. (2022)(19,20). Recruitment through social media channels and patients advocacy groups hindered the estimation of participation rates and may have introduced bias as the biologic therapy use in the US is generally lower than the 47% observed with this study, which may indicate that more patients with prior treatment experiences and more severe disease were enrolled(2) Lastly, this study relied on patients' self-diagnosis and self-rating of their disease severity rather than a clinician assessment. These findings emphasize the importance to understand and account for patients' preferences in research-, clinical-, regulatory- and reimbursement decisions. Future treatments for HS should allow patients to experience more stringent levels of effectiveness than primarily investigated in clinical trials, lead to greater pain reduction, minimize the risk of adverse events when possible, and preferably be offered as oral pill or subcutaneous injection. However, given the observed heterogeneity in patients' preferences, a variety of treatments should become available to allow individualization of HS therapy to patients' unique preferences(12).

6.5. Conclusions

This research presented the results of the first patient preference study with HS patients in the US using a DCE. Faced with high unmet needs and low success rates of limited treatment options available, patients considered effectiveness and pain reduction to be the most important when selecting a treatment. The preferences of patients with HS in the US were revealed to be generally similar to those of patients in Europe. Future HS treatments can be better tailored to the individual needs of patients when accounting for the revealed preferences in decision-making.

6.6. References

1. Montero-Vilchez T, Diaz-Calvillo P, Rodriguez-Pozo JA et al. The Burden of Hidradenitis Suppurativa Signs and Symptoms in Quality of Life: Systematic Review and Meta-Analysis. Int J Environ Res Public Health 2021;18.
2. Garg A, Naik HB, Alavi A et al. Real-World Findings on the Characteristics and Treatment Exposures of Patients with Hidradenitis Suppurativa from US Claims Data. Dermatol Ther (Heidelb) 2022.
3. 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.
4. Ingram JR, Bettoli V, Espy JI et al. Unmet clinical needs and burden of disease in hidradenitis suppurativa: real-world experience from EU5 and US. J Eur Acad Dermatol Venereol 2022.
5. Kjaersgaard Andersen R, Loft IC, Hansen T et al. Incidence and remission rates of self-reported hidradenitis suppurativa - A prospective cohort study conducted in Danish blood donors. J Eur Acad Dermatol Venereol 2022;36:717-725.
6. Dermatology-Times. UCB Announces Positive Phase 3 Studies for Bimekizumab in Hidradenitis Suppurativa. In: Nagorka C, editor, 2022.
7. Kimball AB, Jemec GBE, Alavi A et al. Secukinumab in moderate-to-severe hidradenitis suppurativa (SUNSHINE and SUNRISE): week 16 and week 52 results of two identical, multicentre, randomised, placebo-controlled, double-blind phase 3 trials. Lancet 2023.
8. Martora F, Megna M, Battista T et al. Adalimumab, Ustekinumab, and Secukinumab in the Management of Hidradenitis Suppurativa: A Review of the Real-Life Experience. Clin Cosmet Investig Dermatol 2023;16:135-148.
9. Gaspar K, Hunor Gergely L, Jenei B et al. Resource utilization, work productivity and costs in patients with hidradenitis suppurativa: a cost-of-illness study. Expert Rev Pharmacoecon Outcomes Res 2021:1-10.
10. Ho MP, Gonzalez JM, Lerner HP et al. Incorporating patient-preference evidence into regulatory decision making. Surg Endosc 2015;29:2984-93.
11. Whichello C, Levitan B, Juhaeri J et al. Appraising patient preference methods for decision-making in the medical product lifecycle: an empirical comparison. BMC Med Inform Decis Mak 2020;20:114.
12. Willems D, Hinzpeter EL, Van der Zee HH et al. Patient Preferences in the Management of Hidradenitis Suppurativa: Results of a Multinational Discrete Choice Experiment in Europe. Patient 2023.
13. 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;183:340-348.
14. Willems D, Hiligsmann M, van der Zee HH, Sayed CJ, Evers S. Identifying Unmet Care Needs and Important Treatment Attributes in the Management of Hidradenitis Suppurativa: A Qualitative Interview Study. Patient 2022;15:207-218.

15. Zouboulis CC, Gulliver W, Ingram J et al. Endpoints of clinical trials for Hidradenitis Suppurativa: Proceedings of a round-table session. Exp Dermatol 2020;29 Suppl 1:67-72.
16. 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;179:642-650.
17. Ring HC, Maul JT, Yao Y et al. Drug Survival of Biologics in Patients With Hidradenitis Suppurativa. JAMA Dermatol 2022;158:184-188.
18. Overton PM, Shalet N, Somers F, Allen JA. Patient Preferences for Subcutaneous versus Intravenous Administration of Treatment for Chronic Immune System Disorders: A Systematic Review. Patient Prefer Adherence 2021;15:811-834.
19. Faverio K, Peitsch WK, Gorig T et al. Patient Preferences in Hidradenitis Suppurativa (APProach-HS): a discrete choice experiment. J Dtsch Dermatol Ges 2022;20:1441-1452.
20. Bridges JF, Hauber AB, Marshall D et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health 2011;14:403-13.

7

Economic evaluation of a JAK inhibitor compared to a monoclonal antibody for treatment of moderate-to-severe atopic dermatitis from a UK perspective

Chapter 7 was informed by:
Heinz, K. C., Willems, D., & Hiligsmann, M. (2022). Economic evaluation of a JAK inhibitor compared to a monoclonal antibody for treatment of moderate-to-severe atopic dermatitis from a UK perspective. *Journal of Medical Economics*, 25(1), 491-502.

7.1. Abstract

Aim: Atopic dermatitis (AtD) is a chronic inflammatory skin disorder characterized by severe itching, erythema and scaling, causing pain, stigmatization and social isolation. Despite the growing availability of treatment options, unmet care needs remain. This research aimed to assess the cost-effectiveness of a novel JAK inhibitor (JAKi) compared to a monoclonal antibody and to identify key drivers of cost-effectiveness.

Materials and Methods: A de novo economic model was developed to assess the cost-effectiveness of a novel JAKi compared to an established monoclonal antibody for the treatment of moderate-to-severe AtD patients from a UK perspective. A targeted literature review was conducted to inform the development of the economic model with an advanced model structure. Various scenario- and sensitivity analyses were performed to account for parameter- and structural uncertainty and to identify key drivers of cost-effectiveness.

Results: The JAKi was not cost-effective compared to the monoclonal antibody (£219,733.88 per quality adjusted life year (QALY) gained) at selected price levels when applying the UK willingness-to-pay threshold of £30,000 per QALY gained. Key drivers of cost-effectiveness were utility values, intervention efficacy and drug acquisition costs. A decrease of JAKi's dose costs as well as a lower dose led to cost-effectiveness.

Limitations: Assumptions regarding parameter inputs were necessary, therefore a considerable level of uncertainty regarding efficacy and cost data is to be accounted for in the interpretation of the results. In particular, as the efficacy data were based on single clinical study.

Conclusions: This research revealed the cost-effectiveness of a JAKi compared to a monoclonal antibody for the treatment of moderate-to-severe AtD to be highly sensitive to the costs and effectiveness inputs and identified further cost-effectiveness drivers. It demonstrated that the JAKi could be cost-effective compared to an established monoclonal antibody with a lower dose or a reduced price.

7.2. Introduction

Atopic dermatitis (AtD), which is also referred to as atopic eczema, is a chronic inflammatory skin disorder(1). Displaying point prevalence in adults of 4.4% in the EU (including UK) and 4.9% in the US, AtD belongs to the most common skin diseases(2,3). It is characterized by severe itching, erythema, scaling and sometimes vesiculation and crusting(4). Patients not only experience skin pain, they are also faced with stigmatization, lower self-esteem and social isolation which can cause sleep, depressive or anxiety disorders(5–8). This stress which is caused by AtD reinforces its symptoms, resulting in a vicious cycle(8). Additionally, AtD patients often suffer from further atopic diseases like asthma or allergic rhinitis(7). This high burden not only decreases AtD patients' quality of life, it also causes absenteeism and productivity losses. No laboratory test for the diagnosis of AtD exists(9-11). Instead, AtD is diagnosed by clinical examination and its severity is classified with validated clinical tools like the eczema area and severity index (EASI)(11). For most patients, AtD symptoms last their whole life even though good management can in phases mitigate severity(12). Several options for treating AtD exist. Over the counter (OTC) skin emollients and prescribed topical corticosteroids (TCS) are first line treatment options in the UK, followed by topical calcineurin inhibitors (TCI) in second line and phototherapy as a third line therapy(13). If limited effectiveness is observed or the patient shows more severe symptoms, systemic pharmacotherapy (i.e., oral immunosuppressants) can be prescribed(13). For moderate-to-severe AtD patients, monoclonal antibodies such as dupilumab or Janus kinase inhibitors (JAKi) like baricitinib have represented fifth line therapy options to date(7,13). Despite the availability of these different treatment options for AtD patients with diverse severity levels, optimal treatment for all patients does not exist yet. Current treatments lack practicability as application requires time, is uncomfortable or not all patients fully respond to them(7,13). Considering this treatment gap and the disease burden, it is of clinical and societal importance that new treatments aiming to fulfil unmet care needs are continuously developed(7). Upadacitinib is a novel JAKi and was recently approved for the treatment of moderate-to-severe AtD by the European Commission and the Medicines and Healthcare products Regulatory Agency. It has not yet been recommended for reimbursement by NICE(14-16). Abrocitinib which recently received marketing authorization by the European Commission and the investigational therapy tralokinumab may also contribute to reduce the currently high unmet needs in AtD in the future (17,18). In order for patients to be able to benefit from a developed pharmacological therapy, it must not only be clinically effective to receive marketing authorization, but it also additionally needs a positive reimbursement decision(19). In several countries such as the UK, the relationship

between costs and consequences of new and established therapies in terms of an economic evaluation is a critical element of the Health Technology Assessment (HTA) to decide on the reimbursement of novel therapies(19). Economic models can further reveal the most influential circumstances under which a treatment option can meet the established cost-effectiveness threshold(20). Currently published economic models for AtD treatments did not provide these insights. These economic models either did not include JAKi, did not take the UK National Health Service (NHS) and Personal Social Services (PSS) perspective or used a model structure that could not adequately depict costs and consequences of a JAKi treatment compared to standard of care. Furthermore, new trials that investigated higher treatment responses recently became available, suggesting the need for a new economic model. Therefore, the development of a de novo economic model that considers recent developments in AtD treatment as well as the specific recommendations and reimbursement conditions of the country of interest motivated the aims of this research. The aim of this research was to develop a de novo economic model for moderate-to-severe AtD to conduct an economic evaluation that compares the JAKi upadacitinib to the monoclonal antibody dupilumab from the UK NHS and PSS perspective. It further aimed to identify the key drivers of cost-effectiveness. Such findings were expected to aid decision-makers in the reimbursement deliberations of future treatment options for AtD.

7.3. Methods

7.3.1. Targeted literature review

A targeted literature review (TLR) was conducted to acquire information about the treatment of moderate-to-severe AtD patients with upadacitinib and dupilumab regarding a) treatment efficacy, b) healthcare resource use and costs, c) health-related utilities and d) existing economic evaluations to develop a de novo economic model. First, relevant HTA documents like reports by the Institute for Clinical and Economic Review in the US and, guidelines and technology appraisals (TA) by NICE were searched. Based on the findings, keywords and medical subject heading (MeSH) terms were predefined and connected with Boolean operators to make the subsequent TLR in PubMed more efficient. Only articles published in English no later than September 23, 2021 were considered. The Appendix contains the search strategy. The inclusion and exclusion criteria followed the PICTOS (Population, Intervention, Comparator, Outcome, Timing, Setting / Study Design) framework and are presented in the Appendix using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart(21,22).

7.3.2. Economic evaluation

A Markov cohort model was the preferred modelling technique because it allowed patients to switch between health states, return to, or stay within them for several cycles which was suitable for modelling longer time horizons(19). This was in line with existing economic models concerned with AtD that were published by NICE in TA534 (dupilumab) and TA681 (baricitinib) and by the Institute for Clinical and Economic Review (dupilumab)(13,23,24). These economic models served as reference points during the development of a novel version that included upadacitinib as intervention and used an improved model structure which represented clinical reality more accurately. The economic model took the perspective of UK NHS and PSS and followed therefore NICE's reference case(25). The economic model was developed using the programming language R.

7.3.3. Target population

The characteristics of the target population were obtained from the dupilumab economic model published by NICE in TA534 as this evaluation took the UK perspective(13). The target population thus consisted of adults, i.e., 18 years or older, with moderate-to-severe AtD who have exhausted all previous lines of therapies due to loss of response(13). In line with the dupilumab economic model by NICE in TA534, patients had suffered on average 29 years from the disease at the start of the model(13). The base case population was 38 years old at the start of the economic model(13). 60% of the population were males, 91% were 'white', 50% of the patients suffered from moderate and 50% from severe AtD(13).

7.3.4. Intervention and comparators

Upadacitinib was selected as intervention and compared to the established standard of care in the UK dupilumab(13). Although upadacitinib has not yet been recommended by NICE for the treatment of AtD, it was chosen as the intervention because it is currently the most promising candidate of fifth line treatments for moderate-to-severe AtD, showing higher efficacy than abrocitinib and tralokinumab(26–28). Upadacitinib is a novel JAKi and therefore works differently than dupilumab(29). With upadacitinib as the intervention, the evaluation uses frontier treatments of two available treatment classes.

It is unclear whether a daily oral dosage of upadacitinib 15mg or 30mg will be recommended by NICE. However, upadacitinib 30 mg showed highest efficacy in a randomized controlled trial (RCT) and was therefore chosen in the base case(28). The potential cost-effectiveness of upadacitinib 15 mg was tested in a scenario analysis. The comparator dupilumab is a fully humanized monoclonal antibody (30)

and is prescribed in the UK as fifth line therapy option to moderate-to-severe AtD patients since August 2018(13). According to NICE's recommendations, dupilumab is injected subcutaneously, initially with a loading dose of 600 mg, followed by 300 mg every other week(13). As dupilumab should be combined with TCS and TCI(13), it was assumed that both, upadacitinib 30 mg and dupilumab, were administered as combined therapies. Best supportive care (BSC), which was included as a second line of treatment in this economic model, consisted of phototherapy, psychological support, TCS and TCI(13). All patients, independent of the intervention, were allowed to receive emollients, treatments for flares and seek medical appointments(24).

7.3.5. Model structure

Figure 7-1 depicts this de novo economic model structure. All patients start in the induction phase and receive either dupilumab or upadacitinib 30 mg. Patients with a treatment response, i.e., an improved skin condition of 50-74%, 75-89% or 90-100% after the first cycle, transition to the respective maintenance health state EASI 50, 75 or 90 and receive treatment as long as they maintain this level of response. Patients without response during the induction phase or loss of response in the maintenance health state, stop the intervention and transition to induction of BSC. Patients who achieve at least an EASI 50 after one cycle with BSC transition to BSC EASI 50. Patients without a response or loss of response to BSC transition to no response and remain in their health state until death. All patients can die after each cycle.

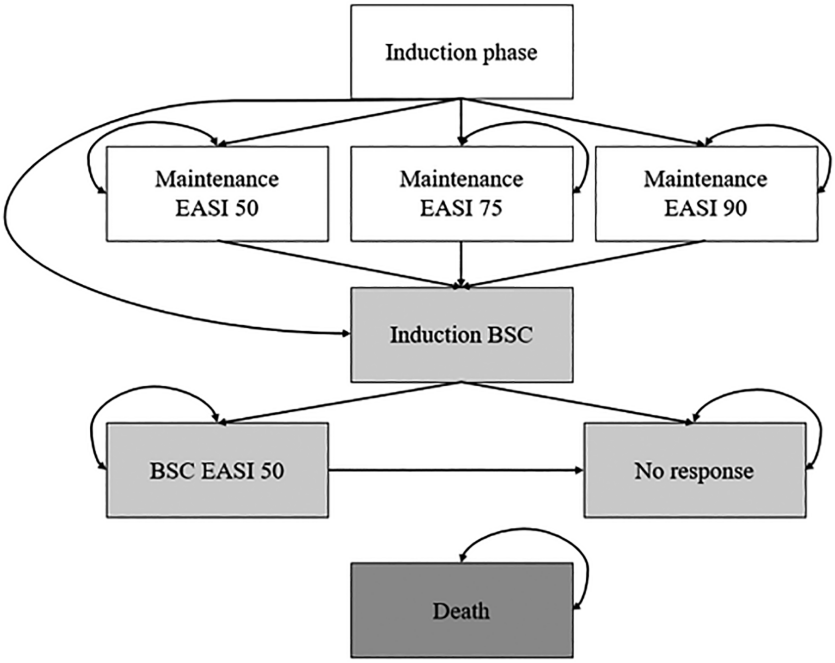


Figure 7 - 1: Model structure.
Note: All patients start in induction phase. Patients can transition to absorbing death health state from any health state. EASI: eczema area and severity index.

The rationales of the underlying assumptions were as follows: First, this de novo economic model incorporated EASI 50, 75 and 90 as three individual response health states because it was difficult to derive efficacy data for combined endpoints as RCTs usually do not report those. Furthermore, the inclusion of a single response health state might not be an appropriate depiction of clinical reality because it could neglect the quality of life and economic benefits that patients with higher response attain. Thus, comparative benefits of a new therapy could be captured probably more accurately by implementing several response health states with response specific utilities and costs. This approach followed the Institute for Clinical and Economic Review(23). Both NICE models defined response to treatment as combined endpoint, consisting of an EASI 50 and an improvement of the dermatology life quality index (DLQI) of 4(13,24). Second, patients could not transition between response health states because it was challenging to obtain probabilities for transitions between response health states. This was in line with the dupilumab economic model published by the Institute for Clinical and Economic Review(23). Third, by implementing an induction health state and a cycle length of 16 weeks, patients could stop receiving the intervention in case of loss of response

every 16 weeks which was in line with NICE's recommendations for the treatment with dupilumab(13). The baricitinib economic model in TA681 also included an induction state but opted for a shorter cycle length of four weeks(24). To model the stopping rule, TA534 prefixed a decision tree before its Markov model which simultaneously increased complexity(13). Fourth, BSC was implemented as a second line of treatment because this approach was taken by the two economic models published by NICE also using the UK perspective(13). The dupilumab economic model by the Institute for Clinical and Economic Review on the other hand included only a no response health state with usual care(23). Fifth, this economic model implemented an absorbing death health state and assumed that neither the disease nor the treatments were associated with a change in mortality. Thus, the chance to die was assumed to be the same in all health states and mortality rates were derived from national life tables. These assumptions were based on the baricitinib economic model by NICE and the dupilumab economic model by the Institute for Clinical and Economic Review(23,24). Sixth, a lifetime horizon was implemented in this economic model as AtD is a chronic condition in line with all three existing economic models(12,13,23,24).

7.3.6. Transition probabilities

The transition probabilities were estimated based on the HeadsUp RCT that was identified during the TLR(31). This head-to-head trial between upadacitinib 30 mg and dupilumab provided the latest efficacy data after 16 and after 24 weeks(31). Other studies that were found during the TLR reported results of either of the two therapies individually against placebo, which were considered less relevant for this economic evaluation(28,30). The response rates after 24 weeks were linearly adjusted for the cycle length of 16 weeks. These transformed numbers served as probabilities for maintaining treatment response. The transition probabilities for the EASI 50 health states could not be derived directly from the HeadsUp trial as they were not reported(31). Therefore, it was assumed that every patient that did not have a high response, needed rescue therapy, discontinued treatment for any reason or died, achieved an EASI 50. This assumption may however, overestimate the proportion of patients that achieve an EASI 50. The HeadsUp study investigated upadacitinib 30 mg and dupilumab as monotherapies which was not in line with NICE's recommendations regarding the treatment with dupilumab suggesting concomitant TCS and TCI(13,31). The EASI 50 response rates for BSC following all interventions were derived from the LIBERTY AD CHRONOS study by taking the placebo EASI 50 response rates as reference point(30). This study investigated the efficacy of dupilumab as combined therapy and included the use of TCS and TCI in all groups, including the placebo group(30). Similar to previous economic

models, neither AtD nor the treatments investigated were assumed to be related to mortality(13,23,24) and thus general mortality rates depending on age and gender were taken from the UK national life table(32). Patients had to stop active treatment or BSC when they did not respond or lost response after 16 weeks, discontinued treatment, had severe side effects that forced a stop, or for which rescue therapy was needed(13,28,30). It was assumed that there was no difference in transition probabilities between moderately and severely affected AtD patients due to lack of distinct numbers. The response rates of dupilumab and upadacitinib 30 mg are presented in Table 7-1.

Table 7 - 1: Transition probabilities.

From	To	Dupi	Upa 30 mg
Induction phase	Maintenance EASI 50	0.1395	0.0805
Induction phase	Maintenance EASI 75	0.2238	0.1034
Induction phase	Maintenance EASI 90	0.3866	0.6063
Maintenance EASI 50	Maintenance EASI 50	0.7735	0.7543
Maintenance EASI 75	Maintenance EASI 75	0.7082	0.7433
Maintenance EASI 90	Maintenance EASI 90	0.6103	0.6774
Induction BSC	BSC EASI 50	0.3746	0.3746
BSC EASI 50	BSC EASI 50	0.6899	0.6899

Note: Probabilities refer to 16-week cycles. Dupilumab and upadacitinib 30 mg numbers were based on HeadsUp(31). BSC numbers were based on LIBERTY AD CHRONOS(30). BSC: best supportive care; dupi: dupilumab; EASI: eczema area and severity index; upa: upadacitinib.

7.3.7. Utilities

The utility values for each health state are presented in Table 7-2. All utilities except for the utilities in the BSC induction and in the no response health state were taken from the dupilumab economic model by the Institute for Clinical and Economic Review that included separated utilities for moderate and severe AtD patients(23). In the induction phase, patients had baseline utility(23). The maintenance EASI 50 and the BSC EASI 50 health state were assumed to have the same utility. Patients that transitioned from intervention to induction of BSC or from BSC to no response were assumed to not immediately return to baseline utility but to have an intermediate utility instead(13). Furthermore, a loss of benefit over time despite maintenance of response was assumed(13). Both assumptions were in line with the dupilumab economic model by NICE in TA534(13). In particular, utility benefit loss started from year 2 with 2%, 5% in year 3, 7% in year 4 and 8% from year 5 onwards in the intervention maintenance health states(13). In the remaining health states, 25% of

the benefit was lost in year 2, 50% in year 3, 75% in year 4 and from year 5 onwards, the patient returned to baseline utility(13).

Table 7 - 2: Utilities

Health state	Utility moderate AtD patients	Utility severe AtD patients
Induction Phase	0.684 (23)	0.535 (23)
Maintenance EASI 50	0.892 (23)	0.882 (23)
Maintenance EASI 75	0.893 (23)	0.890 (23)
Maintenance EASI 90	0.907 (23)	0.911 (23)
Induction BSC	0.821 (13)	0.821 (13)
BSC EASI 50	0.892 (23)	0.882 (23)
No response	0.773 (13)	0.773 (13)
Death	0	0

Note: AtD: atopic dermatitis; BSC: best supportive care; EASI: eczema area and severity index.

7.3.8. Resource use and cost data

The resource utilization inputs were estimated based on TA534 and TA681(13,24). Productivity losses were excluded as those costs are not relevant from an NHS and PSS perspective(33). Unit prices that were relevant for NHS and PSS were assigned(33). Costs were considered in 2020-pound sterling and no conversions were necessary(33). All costs were adjusted according to the NHS cost inflation index (NHSCII) when appropriate(34,35). Both, costs and benefits, were discounted by 3.5% which was in line with NICE's reference case(33). Half-cycle correction was applied. Table 7-3 provides an overview of the resource use and costs per health state and intervention. These could be categorized in 1) intervention costs, 2) other healthcare costs including BSC when applicable and 3) costs for treating adverse events. Although the HeadsUp trial did only present efficacy data for dupilumab and upadacitinib 30 mg as monotherapies, this economic model assumed the occurrence of TCS and TCI costs during intervention(31). A combined therapy was deemed more realistic and was recommended by NICE for the treatment with dupilumab(13). Intervention-specific resources for dupilumab therefore included dupilumab injections, injection training, TCS and TCI and for upadacitinib 30 mg included the medication itself and TCS and TCI(24). Prices for medications were derived from the British National Formulary (BNF)(36). The 30 mg dosage was not approved yet and thus not listed in the BNF(36). Therefore, it was assumed that patients took double the dose of upadacitinib 15 mg(36). Other healthcare costs included costs for emollients, medical appointments, the treatment of flares, phototherapy, psychological support and blood monitoring(24). Costs for

the treatment of adverse events included the treatment of allergic and infectious conjunctivitis and oral herpes in non-intervention states(24). Dupilumab's adverse event resource use consisted of the treatment of injection site reaction, allergic and infectious conjunctivitis and oral herpes(24). JAKi's safety profile was characterized by an immunosuppressive effect(7). Therefore, upadacitinib 30 mg patients were assumed to be at risk for upper respiratory tract infections (URTI)(31). It was assumed that there was no difference in costs between moderate and severe AtD patients due to lack of distinct data.

Table 7 - 3: Resource use and costs

Intervention costs						
Resource type (24)	**Unit price (£)**		**Volume induction**		**Volume maintenance**	
	Dupi	Upa 30	Dupi	Upa 30	Dupi	Upa 30
Treatment	632.45 per dose (36)	28.77 per tablet (36)	9 doses (13)	224 tablets (31)	8 doses (13)	224 tablets (31)
Injection training	56.5 per training (24)		1 (24)	0	0	
TCS	0.11 per gram (36)		1792 gram (24)		896 gram (24)	
TCI	0.74 per gram (36)		28 gram (24)		14 gram (24)	
Other healthcare costs (incl. BSC)						
Resource type (24)	Unit price (£)	Volume induction (24)	Volume maintenance (24)	Volume induction BSC (24)	Volume BSC EASI 50 (24)	Volume no response (24)
Day case admissions (incl. bandages)	455.20 per admission (24)	0.07	0	0.07	0	0.07
Hospitalization episodes	1854.72 per episode (24)	0.04	0.01	0.04	0.01	0.04
Accident and emergency visits	212.67 per visit (37)	0.03	0.01	0.03	0.01	0.03
Dermatologist visits (consultant led)	120.66 per visit (38)	1.88	0.62	1.88	0.62	1.88
Dermatology nurse visits	10.5 per visit (24)	0.17	0.13	0.17	0.13	0.17
GP visits	39 per visit (24)	3.94	0.62	3.94	0.62	3.94
Emollients	6.47 per bottle (36)	104	52	104	52	104
Treatment of flares	4.45 per flare (36)	0	0.14	1.14	1.14	1.14
Full blood count	3.15 per blood count (38)	0	0	1.23	1.23	1.23

Table 7 - 3: Continued.

TCS	0.11 per gram (36)	0	0	1792	896	1792
TCI	0.74 per gram (36)	0	0	28	14	28
Phototherapy courses (22 sessions)	2376.24 per course (38)	0	0	0.02	0.02	0
Psychological support	312.14 per unit (38)	0	0	0.02	0.02	0
Adverse events						
Resource type (24)	Unit price (£) per event	Volume Dupi (24)	Volume Upa 30	Volume BSC and no response (24)		
Injection site reaction	120.66 (38)	0.03	0 [a]	0		
Allergic conjunctivitis	39 (24)	0.12	0 [a]	0.06		
Infectious conjunctivitis	56.02 (24,36,38)	0.08	0 [a]	0.01		
Oral herpes	45.78 (24,36)	0.02	0 [a]	0.03		
URTI	39 (24)	0	0.06 (31)	0		

Note: Numbers were rounded in this table. Volumes apply for 16-week cycles. Emollients consisted of different types of creams (24). Costs adjusted for inflation to 2020 where applicable, using NHSCII (34). [a]No (separated) data available in HeadsUp (31). BSC: best supportive care; Dupi: dupilumab; TCI: topical calcineurin inhibitors; TCS : topical corticosteroids; Upa : upadacitinib; URTI : upper respiratory tract infection.

7.3.9. Results and analyses

Quality adjusted life years (QALY) gained and costs that occurred over the length of the economic model were summed up per intervention and used to calculate the incremental cost-effectiveness ratio (ICER) expressed in costs per QALY gained(33). The WTP threshold set by NICE (£30,000) was used to define cost-effectiveness(33). To account for uncertainty and to identify key drivers of cost-effectiveness, different sensitivity-, scenario,- and threshold analyses were conducted. Several deterministic sensitivity analyses (SA) were performed to reveal to what extent single parameters (including start age, discount rates, time horizon, utilities, costs, efficacy) influenced the cost-effectiveness of the novel JAKi upadacitinib 30 mg(19). Results were depicted in tornado diagrams as recommended by International Society for Pharmacoeconomics and Outcomes Research (ISPOR)(35). To further account for the structural uncertainty, six alternative scenarios were constructed to assess the impact of different structural assumptions of the model on cost-effectiveness estimates. Firstly, a scenario was simulated in which patients in higher response health states, i.e., EASI 75 and EASI 90 were assumed to have lower other healthcare costs due to their improved skin conditions and patients in the no response health state were assumed to have higher healthcare costs due to their worsened skin condition. Secondly, it was assumed that there was no utility loss over time. Thirdly, an alternative model structure was created that included EASI 50 as the only response option similar to the dupilumab and baricitinib economic models published by NICE(13,24). Fourthly, upadacitinib 15 mg instead of upadacitinib 30 mg was compared to dupilumab. Efficacy data for this scenario was derived from Guttman-Yassky et al. (2020)(28). The impact of disease severity on the cost-effectiveness of upadacitinib 30 mg was assessed in a subgroup analysis in scenarios five and six(19,35). The subgroup analysis was difficult to conduct due to lack of distinct data. Thus, only moderately and severely affected patients in terms of utilities perceived in different health states could be assessed separately. As part of the threshold analysis, the value-based price (VBP), i.e., the price for upadacitinib 30 mg to be cost-effective at a certain WTP threshold was calculated for a WTP of £20,000 and £30,000.

7.3.10. Model validation

A TLR was conducted to ensure that relevant data sources were identified. A cross validation based on existing economic dupilumab and upadacitinib 30 mg models published by the Institute for Clinical and Economic Review was conducted as recommended by the ISPOR-SMDM guidelines (23,39,40). Time horizon and discount rates were adjusted when necessary to increase comparability. The costs of the economic models by the Institute for Clinical and Economic Review were not

relevant as these were US-specific. A comparison with TA534 and TA681 was not possible due to censored data(13).

7.4. Results

7.4.1. Base case results

In the base case, upadacitinib 30 mg had higher total QALYs (+0.023) and higher total costs (+£5,103.78) than dupilumab. This yielded an ICER of £219,733.88 (costs per QALY gained) for upadacitinib 30 mg compared to dupilumab, assuming a price of £57.54 per day for upadacitinib 30 mg (36). Considering NICE's WTP threshold of £30,000 per additional QALY gained (33), the JAKi upadacitinib 30 mg was not cost-effective compared to the monoclonal antibody dupilumab. Table 7-4 contains the detailed base case results.

Table 7 - 4: Base case results

Costs and QALYs per intervention		
	Dupi	**Upa 30**
Intervention and adverse event costs	£18,147.46	£23,460.54
Other healthcare costs	£96,433.64	£96,224.34
Total costs	£114,581.10	£119,684.88
Total QALYs	14.124	14.147
ICER		
	Upa 30 vs. Dupi	
ICER	£219,733.88	

Note: dupi: dupilumab; ICER: incremental cost-effectiveness ratio; QALY: quality adjusted life year; upa: upadacitinib.

7.4.2. Deterministic sensitivity analyses

Results of the deterministic SA for upadacitinib 30 mg vs. dupilumab are depicted as tornado diagrams in Figures 7-2 and 7-3. Only the most influential parameters were presented. The analyses showed that utility values in the no response health state and in the maintenance health states had high impact on the ICER. Higher utilities in the no response health state thereby led to a decreased and negative ICER and upadacitinib 30 mg became dominated by dupilumab. Higher utilities in the maintenance health state decreased the ICER as well but simultaneously improved cost-effectiveness of upadacitinib 30 mg. Looking at costs, the most influential parameters were the drug costs of upadacitinib 30 mg and dupilumab. Whereas higher dose costs of upadacitinib 30 mg increased the ICER, higher dose

costs of the comparator dupilumab lowered it and led almost to an ICER below the WTP threshold of £30,000. Lower upadacitinib 30 mg drug costs improved cost-effectiveness and upadacitinib 30 mg became dominant compared to dupilumab. The efficacy tornado diagram in Figure 7-3 shows that the probabilities to achieve or maintain a certain response with both drugs had remarkable impact. The increase of the probability to achieve an EASI 90 with dupilumab thereby had the highest impact and led to an increased ICER. An increased probability to maintain an EASI 90 with dupilumab, however, led to a lower and negative ICER. This pattern could be observed for the following dupilumab efficacy values as well. When the efficacy values of upadacitinib 30 mg were increased, the ICER decreased for all parameters while a decrease led to a higher ICER with the exception of the probabilities to achieve or maintain an EASI 90. Here, lower efficacy numbers led to negative ICERs, i.e., dupilumab dominated upadacitinib 30 mg.

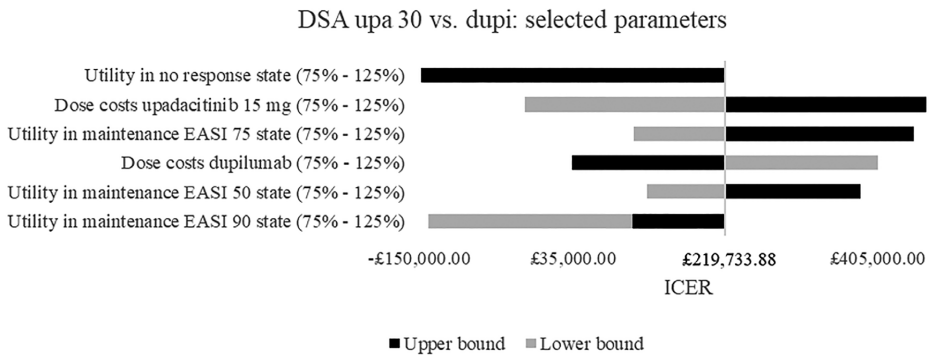


Figure 7 - 2: Deterministic sensitivity analyses of selected parameters.
Note: Upper bound of utility in no response was -£35,198,512.55. DSA: deterministic sensitivity analyses; dupi: dupilumab; EASI: eczema area and severity index; ICER: incremental cost-effectiveness ratio; upa: upadacitinib.

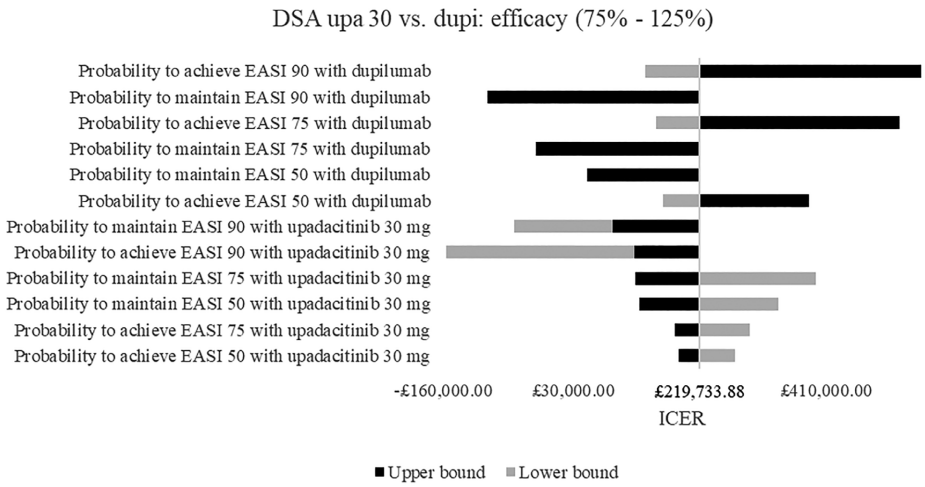


Figure 7 - 3: Deterministic sensitivity analyses of efficacy parameters.
Note: Upper bound of probability to achieve EASI 90 with dupilumab was £1,735,169.38. DSA: deterministic sensitivity analyses; dupi: dupilumab; EASI: eczema area and severity index; ICER: incremental cost-effectiveness ratio; upa: upadacitinib.

7.4.3. Scenario analyses

Table 7-5 presents the results of the six alternative scenarios. When reduced other healthcare costs in higher response health states and higher other healthcare costs in the no response health state were assumed, the ICER decreased slightly. Even though cost-effectiveness did not change in this case, the results showed that implementing several response levels with differing costs instead of only one response level could increase modelling precision. The second scenario assumed that there was no utility loss over time. Consequently, the no response health state became relatively better and the benefit between intervention and comparator decreased, leading to an increased ICER. The next scenario analysis where only one endpoint, i.e., EASI 50 was implemented instead of three led to a negative ICER, i.e., upadacitinib 30 mg was dominated by dupilumab and showed that the number of included response health states could impact the results. The fourth scenario compared a lower dose of upadacitinib to dupilumab. This resulted in lower costs and QALYs than dupilumab and a decreased but positive ICER. Nevertheless, upadacitinib 15 mg could be regarded as cost-effective compared to dupilumab when a willingness to accept threshold of £30,000 was assumed because the savings per QALY sacrificed were above that threshold. When only severe AtD patients were considered, the cost-effectiveness improved as severely affected patients were expected to achieve a relatively higher benefit from a successful treatment. However, the ICER was still above the WTP threshold of £30,000/QALY. When only moderately affected AtD patients were included, the ICER increased.

Table 7 - 5: Scenario analyses

Scenario	ICER
Base case	£219,733.88
Lower other healthcare costs in higher response health states and higher other healthcare costs in no response health state	£210,102.61
No utility loss over time	£392,033.85
No EASI 75 and 90 response options	-£854,472.36
Upa 15 mg vs. dupilumab	£129,606.91*
Only moderate AtD	£292,375.71
Only severe AtD	£176,004.83

Note: The table presents the ICERs which resulted from the respective scenarios.
**Upa 15 mg led to less costs and less QALYs than dupilumab. AtD: atopic dermatitis; dupi: dupilumab; EASI: eczema area and severity index; ICER: incremental cost-effectiveness ratio; upa: upadacitinib.*

7.4.4. Threshold analysis

In the base case, it was assumed that upadacitinib 30 mg costs £57.54 per day(36). The VBP presented in Table 7-6 revealed that the drug acquisition costs per day may not exceed £46.35 to reach cost-effectiveness, considering a WTP threshold of £30,000. Conversely, the price per day for upadacitinib 30 mg needs to be reduced by 19.5% in order for upadacitinib 30mg to be cost-effective compared to dupilumab, considering a WTP threshold of £30,000.

Table 7 - 6: Threshold analysis

	Price per day upa 30 mg	% reduction in price of upa 30 mg to be cost-effective
Base case price	£57.54	-
VBP (WTP £20,000)	£45.76	20.5%
VBP (WTP £30,000)	£46.35	19.5%

Note: upa: upadacitinib; VBP: value-based price; WTP: willingness-to-pay.

7.4.5. Model validation

The economic model published by the Institute for Clinical and Economic Review yielded total QALYs of 16.28 for the treatment with dupilumab, applying a discount rate of 3%(23). This de novo economic model resulted in a total of 14.12 QALYs for dupilumab when the same discount rate was considered. The difference could be explained by the utility loss which was not assumed in the economic model by the Institute for Clinical and Economic Review(23). An updated economic evaluation

published by the Institute for Clinical and Economic Review yielded total QALYs of 3.43 for dupilumab when the economic model run for five years and a 3% discount rate was applied(39). Under these circumstances, the presented economic model resulted in 3.39 QALYs and thus was similar to the existing economic model. The same updated economic model resulted in 3.35 QALYs for upadacitinib 30 mg while the de novo economic model yielded a similar value of 3.41 QALYs(39).

7.5. Discussion

This economic evaluation revealed that the JAKi upadacitinib 30 mg led to slightly higher QALYs than the biological drug dupilumab at higher costs. These higher costs were not caused by a higher price per dose but by a much higher administration frequency of upadacitinib compared to dupilumab. At the assumed price, upadacitinib 30 mg was found not to be cost-effective compared to dupilumab when a WTP threshold of £30,000 was applied. The analyses further showed that the key drivers of cost-effectiveness were utility values of the no response, and the maintenance health states, drug costs of upadacitinib 30 mg and dupilumab, and efficacy of both interventions, in particular the probability to achieve an EASI 90 response with dupilumab. With a decrease of upadacitinib 30 mg's dose costs by approximately 20%, cost-effectiveness could be demonstrated. Efficacy data was based on a study where upadacitinib 30 mg was administered as monotherapy. The real efficacy of a combined therapy could be higher and, as revealed by the SAs, would improve the cost-effectiveness. This is the case for dupilumab as well but the SAs showed that an increase of the probability to maintain a low response with dupilumab could also decrease the ICER and increase cost-effectiveness of the JAKi. This unexpected finding probably occurred because the costs of staying in the dupilumab EASI 50 health state were relatively greater than the QALYs gained in this low response health state. An exclusion of the EASI 75 and 90 response health states for both interventions led to a negative ICER as well and thus to dominance of dupilumab compared to upadacitinib 30 mg. This might be the case because the efficacy of dupilumab for a low response was higher as the dropout rate was lower. The scenarios showed that the inclusion and exclusion of response health states could have a huge impact on the results. Interestingly, the comparison of a lower dose of the JAKi (15mg) to the biological drug led to cost-effectiveness of the JAKi. The QALYs gained with upadacitinib 15 mg were lower but the costs were lower as well.

This economic evaluation had several strengths. The model validation showed that the QALYs of this de novo economic model were similar to other economic models'

QALYs. Due to the inclusion of the relatively new JAKi upadacitinib 30 mg and the monoclonal antibody dupilumab which is the current standard of care, the economic model can be considered as being up to date. Furthermore, the hybrid model structure combined the advantages of several economic models and therefore a more precise and realistic analysis was possible. Three instead of one endpoint were incorporated into the economic model. Thus, the economic model accounted for higher quality of life benefits that occurred in higher response health states allowing a more accurate prediction of the costs and health benefits of both treatments. The need to implement more than one response health state was supported by the third scenario analysis which included only one EASI 50 maintenance health state and was similar to AtD economic models published by NICE(13,24). The analysis showed that this approach could lead to an underestimation of the cost-effectiveness of the intervention (here upadacitinib 30 mg) which in turn can incorrectly inform research and development (R&D) or reimbursement decisions. Therefore, it was probably correct to include three response health states like the dupilumab economic model by the Institute for Clinical and Economic Review did instead of following NICE's opinion that one response level would be sufficient(13,23,24). The cycle length of 16 weeks combined with the two induction health states increased precision and could consider NICE's recommendation to stop the intervention in case of no response after 16 weeks(13). At the same time, it decreased complexity as a pre-fixed decision tree like in TA534 was not needed(13). The use of a replicated dupilumab economic model published either by NICE in TA534 or by the Institute for Clinical and Economic Review would have probably led to a false ICER, the true key drivers of cost-effectiveness not being identified and in case of the second economic model, the UK NHS and PSS perspective not being represented appropriately. Therefore, the combination of the existing economic models increased reliability of the analyses and their results. It was in general difficult to find input data for the economic model but due to the TLR probably all data sources available could be identified. The inclusion of a second line of treatment with BSC before a final no response health state made the economic model and its results more realistic from a clinical practice perspective. Various analyses addressed the structural uncertainty and although it was difficult to agree on input data and to make reasonable structural model assumptions where no data was available, important insights regarding the cost-effectiveness of two drugs with different modes of operations were revealed.

Nevertheless, this economic evaluation also had limitations. The model structure did not allow patients to switch between response health states. It therefore indirectly assumed that a patient immediately falls below an EASI 50 when not achieving EASI 90. This may, however, not represent clinical reality correctly. Furthermore,

the available data to develop the economic model were limited. TA534 and TA681 were censored which also impeded the external model result validation(13,24). Efficacy data for dupilumab, upadacitinib 30 mg and BSC were based on single studies(30,31). Those studies did not consider the stopping rule that was assumed in the economic model and led to a discontinuation when the patient did not respond or lost response after 16 weeks(30,31). Moreover, the dupilumab and upadacitinib 30 mg response rates were available for 16 and 24 weeks whereas the BSC response rates were available for 16 and 52 weeks(30,31). Additionally, the HeadsUp trial that was used for the transition probabilities of dupilumab and upadacitinib 30 mg did not report EASI 50(31). The necessary assumptions to obtain the respective transition probabilities anyway might have led to an overestimation of the proportion of patients that achieve and maintain an EASI 50 while being treated with either dupilumab or upadacitinib 30 mg. Furthermore, the HeadsUp trial investigated dupilumab and upadacitinib 30 mg as monotherapies(31). However, NICE recommends dupilumab to be administered as a combined therapy with TCS and TCI(13). The use of TCS and TCI during intervention were included in the costs of the respective health states to at least depict this part in a more realistic way. The types of adverse events and their rates of occurrence were mainly derived from TA681(24). Those were, however, not in line with the study results(30,31). As a result, costs and consequences caused by the occurrence of adverse events might be underestimated for all interventions. Furthermore, the study only incorporated the effects of upadacitinib and dupilumab on AtD. As many patients have comorbidities such as asthma or allergic rhinitis, and both drugs could alleviate the symptoms of these comorbidities, this might impact the cost-effectiveness of the respective drug(7). No data for resource use of different response levels were available and thus it was assumed that costs for maintenance EASI 50, 75 and 90 were the same but this assumption could be incorrect. Due to a lack of distributions, no probabilistic sensitivity analysis (PSA) could be conducted. Finally, most data were not available separately for subgroups. Performing subgroup analyses was therefore restricted.

This research suggested that the existing NICE approved AtD economic models are no longer sufficient for the evaluation of new interventions. Novel treatment options for AtD like upadacitinib aim for higher treatment responses than EASI 50. This is reflected by newer trials which report newer endpoints. Additionally, Silverberg et al. (2021) concluded that higher EASI improvements lead to higher improvements in patient-reported outcome measures(41). Economic models need to accommodate to these changes and new findings. Therefore, the use of only one combined endpoint does not meet the requirements of new interventions anymore, a fact that US-specific economic models already consider(23,37). On the other hand,

it is needed to stick closely to the existing AtD economic models published by NICE to account for the UK NHS and PSS perspective. Therefore, complete replication of US economic models is not feasible either. However, the combination of the advantages of existing economic models led to a complex model structure. While this probably depicts clinical reality more accurately, it might at the same time not live up to the purpose of a model which is to simplify reality. This is accompanied by the difficulty to obtain input data as data for a total of eight health states and corresponding transitions is needed, the cycle length of 16 weeks is relatively short and the stopping rule is a feature that is not commonly accounted for in RCTs. While further data generation of AtD treatments, especially on long-term treatment response and compliance, may reduce treatment-specific parameter uncertainty, patient and clinical expert opinion must be considered to address uncertainties on structural model parameters and assumptions for future economic analyses. Additionally, the data censoring of important HTA evidence hampered replication and cross validation and will continue to do so in the future. By reporting in greater detail input data and results, future economic models could build upon existing models and external validation could be simplified. This would result in improved quality of economic models and more accurate results that can better inform decision-making.

7.6. Conclusions

While this de novo economic model demonstrated that the JAKi upadacitinib 30 mg was not cost-effective compared to the standard of care dupilumab under base case assumptions, key cost and health effect drives were highlighted in various sensitivity analyses. Utility values, intervention efficacy and drug acquisition costs were most influential for upadacitinib 30 mg to be cost-effective compared to dupilumab. Furthermore, the scenario and threshold analyses demonstrated that using half of the dose of upadacitinib or reducing the daily drug acquisition costs of upadacitinib 30 mg by 20% led to cost-effectiveness of the JAKi. This research additionally exposed a critical limitation of replicating pre-existing models for AtD. The improved AtD economic model and the gained insights could help the industry to make informed R&D decisions to develop the required evidence to allow investigational products to achieve future reimbursement to reduce AtD patients' currently high unmet care needs. More robust clinical, cost and quality of life data in the future will allow more accurate simulation of the cost-effectiveness of therapies in AtD and will enable suitable differentiation strategies.

7.7. References

1. Silverberg JI, Hanifin JM. Adult eczema prevalence and associations with asthma and other health and demographic factors: a US population-based study. J Allergy Clin Immunol. 2013;132:1132–1138.
2. Barbarot S, Auziere S, Gadkari A, et al. Epidemiology of atopic dermatitis in adults: Results from an international survey. Allergy. 2018;73.
3. Avail Dermatology. Top 5 Most Common Skin Conditions [Internet]. 2018. [cited 2021 Jun 10]. Available from: https://availdermatology.com/common-skin-conditions/
4. Williams HC, editor. Atopic dermatitis: The epidemiology, causes, and prevention of atopic eczema. Cambridge: Cambridge University Press; 2000.
5. Vakharia PP, Chopra R, Sacotte R, et al. Burden of skin pain in atopic dermatitis. Ann Allergy Asthma Immunol. 2017;119:548-552.e3.
6. Cheng C-M, Hsu J-W, Huang K-L, et al. Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: a nationwide longitudinal study. J Affect Disord. 2015;178:60–65.
7. Love I, White K. Atopic Dermatitis / Atopic Eczema: Disease Landscape & Forecast. Decision Resources Group. 2020.
8. Senra MS, Wollenberg A. Psychodermatological aspects of atopic dermatitis. Br J Dermatol. 2014;170 Suppl 1:38–43.
9. Silverberg JI, Gelfand JM, Margolis DJ, et al. Patient burden and quality of life in atopic dermatitis in US adults: A population-based cross-sectional study. Ann Allergy Asthma Immunol. 2018;121:340–347.
10. Ariëns LFM, van Nimwegen KJM, Shams M, et al. Economic Burden of Adult Patients with Moderate to Severe Atopic Dermatitis Indicated for Systemic Treatment. Acta Derm Venereol. 2019;99:762–768.
11. Frazier W, Bhardwaj N. Atopic Dermatitis: Diagnosis and Treatment. Am Fam Physician. 2020;101:590–598.
12. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. The Lancet. 2020;396:345–360.
13. National Institute for Health and Care Excellence. Dupilumab for treating moderate to severe atopic dermatitis: Technology appraisal guidance [TA534] [Internet]. 2018. [cited 2021 Jun 10]. Available from: https://www.nice.org.uk/guidance/TA534
14. European Medicines Agency. Rinvoq: upadacitinib [Internet]. 2021. [cited 2021 Dec 19]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/rinvoq
15. Medicines and Healthcare products Regulatory Agency. SUMMARY OF PRODUCT CHARACTERISTICS [Internet]. 2021. [cited 2021 Oct 23]. Available from: https://mhraproducts4853.blob.core.windows.net/docs/9890d20041d9d6b42d1d098c89bfe58333260ad7
16. National Institute for Health and Care Excellence. Upadacitinib for treating moderate to severe atopic dermatitis in people aged 12 and over [ID3733]: In development [GID-TA10597] [Internet]. 2021. [cited 2021 Jun 10]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10597
17. European Medicines Agency. Cibinqo: abrocitinib [Internet]. 2021. [cited 2021 Dec 19]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/cibinqo

18. National Institute for Health and Care Excellence. Tralokinumab for treating moderate to severe atopic dermatitis [ID3734]: In development [GID-TA10596] [Internet]. 2021. [cited 2021 Jun 28]. Available from: https://www.nice.org.uk/guidance/indevelopment/gid-ta10596
19. Drummond MF, Sculpher M, Claxton K, et al. Methods for the economic evaluation of health care programmes. 4th edn. Oxford: Oxford University Press; 2015.
20. Ling DI, Lynd LD, Harrison M, et al. Early cost-effectiveness modeling for better decisions in public research investment of personalized medicine technologies. Journal of Comparative Effectiveness Research. 2019;8.
21. Nelson HD. Systematic Reviews to Answer Health Care Questions. Philadelphia: Wolters Kluwer Health; 2014.
22. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372.
23. Institute for clinical and economic review. Dupilumab and Crisaborole for Atopic Dermatitis: Effectiveness and Value [Internet]. 2017. [cited 2021 Jul 4]. Available from: https://icer.org/wp-content/uploads/2020/10/MWCEPAC_ATOPIC_EVIDENCE_REPORT_051217.pdf
24. National Institute for Health and Care Excellence. Baricitinib for treating moderate to severe atopic dermatitis: Technology appraisal guidance [TA681] [Internet]. 2021. [cited 2021 Jun 10]. Available from: https://www.nice.org.uk/guidance/ta681
25. Mauskopf J, Chirila C, Birt J, et al. Drug reimbursement recommendations by the National Institute for Health and Clinical Excellence: have they impacted the National Health Service budget? Health Policy. 2013;110:49–59.
26. Simpson EL, Sinclair R, Forman S, et al. Efficacy and safety of abrocitinib in adults and adolescents with moderate-to-severe atopic dermatitis (JADE MONO-1): a multicentre, double-blind, randomised, placebo-controlled, phase 3 trial. The Lancet. 2020;396:255–266.
27. Wollenberg A, Blauvelt A, Guttman-Yassky E, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol. 2021;184:437–449.
28. Guttman-Yassky E, Thaçi D, Pangan AL, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020;145:877–884.
29. Parmentier JM, Voss J, Graff C, et al. In vitro and in vivo characterization of the JAK1 selectivity of upadacitinib (ABT-494). BMC Rheumatol. 2018;2.
30. Blauvelt A, Bruin-Weller M de, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. Lancet. 2017;389:2287–2303.
31. Blauvelt A, Teixeira HD, Simpson EL, et al. Efficacy and Safety of Upadacitinib vs Dupilumab in Adults With Moderate-to-Severe Atopic Dermatitis: A Randomized Clinical Trial. JAMA dermatology. 2021;157:1047–1055.

32. Office for National Statistics. National life tables: UK [Internet]. 2021. [cited 2021 May 6]. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesunitedkingdomreferencetables
33. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013 [Internet]. 2013. [cited 2021 Jun 10]. Available from: https://www.nice.org.uk/process/pmg9/chapter/foreword
34. Curtis L, Burns A. Unit Costs of Health and Social Care 2019 | PSSRU [Internet]. 2019. [cited 2021 Jun 6]. Available from: https://www.pssru.ac.uk/project-pages/unit-costs/unit-costs-2019/
35. Husereau D, Drummond M, Petrou S, et al. Consolidated Health Economic Evaluation Reporting Standards (CHEERS)--explanation and elaboration: a report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force. Value Health. 2013;16:231–250.
36. National Institute for Health and Care Excellence. BNF British National Formulary [Internet]. 2021. [cited 2021 May 6]. Available from: https://bnf.nice.org.uk/
37. National Health Service. National tariff payment system documents, annexes and supporting documents [Internet]. 2020. [cited 2021 Jun 10]. Available from: https://www.england.nhs.uk/publication/national-tariff-payment-system-documents-annexes-and-supporting-documents/
38. National Health Service. National cost collection for the NHS [Internet]. 2019. [cited 2021 Jun 10]. Available from: https://www.england.nhs.uk/national-cost-collection/
39. Institute for clinical and economic review. JAK inhibitors and monoclonal antibodies for the treatment of atopic dermatitis: effectiveness and value [Internet]. 2021. [cited 2021 Jul 4]. Available from: https://icer.org/wp-content/uploads/2020/12/ICER_Atopic-Dermatitis_Draft-Evidence-Report_051421.pdf
40. Eddy DM, Hollingworth W, Caro JJ, et al. Model transparency and validation: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force-7. Med Decis Making. 2012;32:733–743.
41. Silverberg JI, Lei D, Yousaf M, et al. What are the best endpoints for Eczema Area and Severity Index and Scoring Atopic Dermatitis in clinical practice? A prospective observational study. Br J Dermatol. 2021;184:888–895.

7.8. Appendix

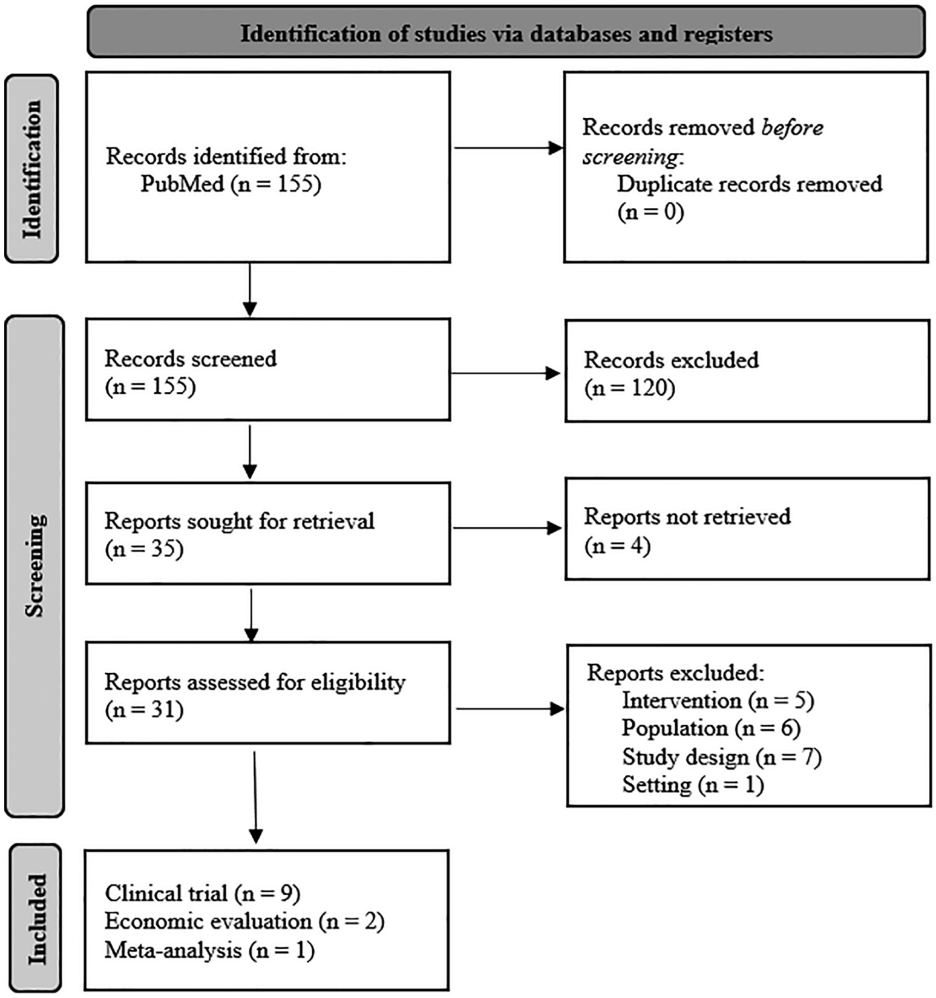
Appendix Table 7 - 1: Search strategy.

(“dermatitis, atopic”[Mesh] OR “Eczema”[Mesh] OR “atopic dermatitis”[all fields] OR (“atopic”[all fields] AND “dermatitis”[all fields]) OR “atopic eczema”[all fields] OR (“atopic”[all fields] AND “eczema”[all fields]) OR “eczema”[all fields]) AND (“2000/01/01”[PDAT] : “2021/09/23”[PDAT]) AND (english[Language]) AND (“dupilumab”[tiab] OR “dupixent”[tiab] OR “upadacitinib”[tiab] OR “rinvoq”[tiab]) AND (“Health Resources”[Mesh] OR “Health Care Costs”[Mesh] OR “Costs and Cost Analysis”[Mesh] OR “Hospital Costs”[Mesh] OR “Drug Costs”[Mesh] OR “Cost of Illness”[Mesh] OR “Health Expenditures”[Mesh] OR “hospitalization”[Mesh] OR “hospitals”[Mesh] OR “resource*”[tiab] OR “cost*”[tiab] OR “expenditure*”[tiab] OR “economic burden”[tiab] OR (“economic”[tiab] AND “burden”[tiab]) OR “health service use”[tiab] “healthcare service use”[tiab] OR “health care service use”[tiab] OR “healthcare service utilization”[tiab] OR “health care service utilization”[tiab] OR “healthcare utilization”[tiab] OR “health utilization”[tiab] OR “hospital”[tiab] OR “hospital stay”[tiab] OR “drug use”[tiab] OR “drug utilization”[tiab] OR “healthcare use”[tiab] OR “health care use”[tiab] OR “health use”[tiab] OR “visit*”[tiab] OR “appointment*”[tiab] OR “Randomized Controlled Trials as Topic”[Mesh] OR “randomized controlled trial”[Publication Type] OR “randomised controlled trial”[tiab] OR “randomization”[tiab] OR ”randomisation”[tiab] OR “RCT”[tiab] OR “Clinical Trial”[publication type] OR “Clinical Trials as Topic”[Mesh] OR ”Controlled Clinical Trial”[publication type] OR “clinical trial*”[tiab] OR (“clinical”[tiab] AND “trial*”[tiab]) OR “Cost-Benefit Analysis”[Mesh] OR “Models, Economic”[Mesh] OR “economic evaluation*”[tiab] OR “cost effectiveness”[tiab] OR “CEA”[tiab] OR “cost utility”[tiab] OR “CUA”[tiab] OR “economic model*”[tiab] OR “cost minimization”[tiab]) NOT (“child*”[title]) NOT (“review”[publication type])

Appendix Table 7 - 2: Inclusion and exclusion criteria.

	Inclusion	**Exclusion**
Population	• Humans • Diagnosed with moderate-to-severe AtD • 18 years or older	• Non-humans • Not diagnosed with moderate-to-severe AtD • Younger than 18 years
Intervention	• Dupilumab, 300 mg bi-weekly • Upadacitinib	• Neither dupilumab nor upadacitinib included in treatment
Comparator	• Conventional treatments for AtD • Placebo • None	• Treatments not mentioned in inclusion
Outcome	• Resource use / costs • Effectiveness / Efficacy: At least EASI or adverse events • ICER	• Articles only reporting about productivity loss and / or out-of-pocket expenditures • Articles only reporting about utilities / quality of life, laboratory parameters • None of the outcomes mentioned in inclusion reported
Timing	Published between January 1, 2000 and April 5, 2021	Published before January 1, 2000 or after April 5, 2021
Study design	All, except those mentioned in exclusion, but preferred: • RCTs • Clinical trials • Economic evaluations	• Editorials • Expert reports • Case studies / series • Reviews • Cohort studies • Retrospective studies • Papers about not yet conducted research • Letters, position papers • Validation Studies • Guidelines • Ad hoc analyses • Evaluation of studies • Pooled analyses • Summaries • Comments • Observational studies
Setting	Europe, North-America	Articles not reporting about countries mentioned in inclusion
Language	English	Articles not available in English
Availability	Articles available as full text	Articles not available as full text

Note: AtD: Atopic dermatitis, RCT: Randomized controlled trial.



Appendix Figure 7 - 1: PRISMA Diagram. Note: Based on Page et al. (2021) (21).

8

General Discussion

Chronic inflammatory skin diseases are recognized to be among the most common health problems worldwide and have profound physical, emotional and financial consequences for patients, families and society. Although patient-centric research into the burden, unmet care needs and preferences in chronic inflammatory skin diseases has increased in recent years, there remains a lack of research to enable the disease management to better address the holistic needs of patients. Health economics as scientific area of research has the potential to guide policy-makers towards a more efficient allocation of resources to improve the disease management of chronic inflammatory skin diseases within a healthcare system. By generating first-hand evidence or synthesizing evidence from different sources to predict the clinical and socio-economic consequences of policy-decisions, health economics can contribute to more resource-efficient decision-making by clinicians, payers and politicians. This dissertation presents novel health economics research that aimed to advance the scientific understanding of the unmet care needs, treatment preferences and health economic implications of chronic inflammatory skin disease management to contribute towards improving management outcomes.

8.1. Main objectives and results

This dissertation intended to study the health economic implications, unmet care needs and preferences of patients and physicians with some of the most common and burdensome chronic inflammatory skin disorders, namely, psoriasis (PSO), atopic dermatitis (AtD) and hidradenitis suppurativa (HS). Existing patient preference studies in PSO and HS were identified and novel qualitative and quantitative insights in HS were generated. Additionally, the cost-effectiveness of two treatment candidates in AtD and HS using 'de novo' economic models was predicted. These findings were intended to allow better informed clinical-, development- and reimbursement decision-making to address the elicited patient needs with enhanced disease management through individualized treatment approaches.

As presented in this dissertation, it was concluded that the diverse unmet care needs and preferences of patients and physicians in PSO were not fully satisfied despite numerous treatments being available(1). The diversity of preferences revealed in PSO indicated the importance to continue the development of a variety of interventions to allow individualization of patient care. In HS, a lack of available patient-centric studies allowed the generation of unprecedented qualitative and quantitative insights on the unmet care needs and treatment preferences form the perspectives of patients and physicians(2). Important differences in perceptions of unmet care needs and treatment preferences between patients and physicians and

across geographies with different care pathways were unveiled. In HS, the identified unmet care needs and treatment preferences were understood to be driven by low effectiveness of the few available treatment options which often leave patients with uncontrolled flares, pain and disease progression(3,4). Furthermore, two 'de novo' developed health economic models revealed under which health benefits and costs two treatment candidates for HS and AtD could be considered cost-effective to enable their future reimbursement to improve disease management outcomes(5,6).

8.2. Contribution to scientific debate

In contrast to previous systematic literature reviews (SLR) of discrete-choice experiments (DCEs) in PSO which already provided a general overview of patient preferences, the SLR presented in this dissemination evaluated the treatment attributes that patients and physicians considered the most important in PSO and additionally appraised the quality of included DCEs using recommended evaluation tools(1,7,8). This study confirmed findings of previous SLRs reporting efficacy to be the most influential treatment attribute for both patients and physicians. Furthermore, actionable recommendations to increase transparency on non-responders, to consider interviewer-led administration and better, to better justify the experimental design, and to perform more frequent pilot-testing were formulated to strengthen the methodology of future DCEs in PSO.

The early cost-effectiveness research in HS critically appraised existing economic evaluations in HS to subsequently develop a 'de-novo' early cost-effectiveness model to assess the potential cost-effectiveness of a treatment candidate for HS(5). This research added value to existing evidence by estimating the possible economic value, i.e., the cost-effectiveness of a treatment candidate that had not been appraised before. It additionally explored key drivers of cost-effectiveness to contextualize under which evidence and price levels future treatments for HS can expect to achieve favourable cost-effectiveness outcomes for reimbursement. Discontinuation rates, model time horizon, treatment acquisition costs, dosing and efficacy were determined to be most influential in cost-effectiveness analyses in HS.

The scarcity of patient-centric research in HS observed during the review of evidence for the cost-effectiveness research stimulated the development of unprecedented qualitative and quantitative patient preference research in HS(2-4). Firstly, the qualitative research in the form of semi-structured interviews with patients with HS and physicians supported the growing understanding of the unmet care needs beyond what was previously studied to limited degree and additionally formulated

recommendations for complementary quantitative preference research(9). Across the few available studies in HS, the level of unmet care need was consistently reported to be high, with pain, physical burden and HS-specific QoL being the most apparent domains of unmet care needs(10,11).

The findings of the interviews and previous research were then implemented for the development of the first multi-national DCE questionnaire with HS patients in Europe which aimed to reveal the most important treatment attributes in treatment decision-making(4). In parallel to this research, the first DCE published with German HS patients also reported therapeutic success to be the most important treatment attribute with safety to be less important(12).

As the transferability of stated preferences in HS across geographies had not been studied, a similar DCE with US patients was conducted to reveal their preferences in treatment decision-making(3). The treatment preferences between patients enrolled in the different DCEs in Europe, Germany and the US were similar by emphasizing effectiveness and pain control to be most important with safety outcomes being less important(3,4,12).

Lastly, the 'de novo' cost-effectiveness model in AtD was developed based on the shortcomings of previous research identified by a targeted literature review(6). Namely, this research was the first to explore the cost-effectiveness of a Janus Kinase (JAK) inhibitor from a UK perspective against standard of care and addressed previous limitations of not exploring influential circumstances influential circumstances under which a treatment candidate can meet the established cost-effectiveness thresholds. Furthermore, the novel model structure combined the advantages of several previous economic models by incorporating three instead of one response endpoint which was expected to lead to a more precise and realistic simulation of health and cost consequences of included interventions.

8.3. Methodological key considerations / reflections

The robustness of the SLR of DCEs in PSO allowed to confirm that DCEs remain the standard tool in quantitative preferences elicitation(1). The applied SLR methodology was considered robust by using the PREFS checklist supplemented by 4 items from the ISPOR checklist to appraise the quality of included DCEs(13,14). However, using different checklists or evaluating in detail the data-collection and statistical analysis plans of other DCEs could have revealed further methodological learnings. A further gap observed with the SLR of DCE literature was the lack of reporting

on non-responders, which could have indicated the adequateness of the surveys used. Most studies also omitted reporting coefficient scores for all attributes or simply interpreted coefficient scores without considering the range of the levels. Additionally, including conference proceedings would have allowed up to 12 further abstracts to be appraised for inclusion, but would have likely led to uncertainty due to common word limit of conference abstracts. The growing number of DCE studies highlighted the importance of repeating SLRs in the future to capture and synthesize new evidence as it becomes available, which can already be observed by the increasing applications of living systematic reviews.

In the early cost-effectiveness analyses of a treatment candidate HS, censoring of clinical and economic evidence of a previous economic model prevented a more accurate replication and validation of results as two of the model health states could not be populated(5). Previously published 5-health statement models had to be scrutinized to a binary response model by using a 3-health state model (including the absorbing 'death' state)(15). This discrepancy of model structure (3 vs. 5 health state model) was considered to have contributed to differing proportions of responders and their associated cumulative costs and QALYs. The discrepancy also hindered accurate external validity testing against previously published models. However, extensive scenario and sensitivity analyses were conducted in an effort to estimate the magnitude of change in costs and health benefits different model health states could have resulted in. At time of this research, only little real-world evidence data of existing treatments in HS existed, which hindered to validate the economic model estimation against observations in real life on e.g., patients' resource utilization, disease progression or treatment discontinuation, which would have led to greater credibility of the economic model outcomes for future healthcare decision-making.

The semi-structured interviews to elicit the unmet care needs of physician and patients with HS followed established qualitative research practices but may have been subject to selection bias(2). Selection bias is a common limitation of qualitative research with small samples, but the recruitment was pre-defined to be terminated only once the results became repetitive, which was assumed to indicate response saturation(16). In addition, enrolment of broader profiles than patients, dermatologists or surgeons like general practitioners, nurses or informal care givers could have provided more diverse perspectives on the unmet care needs in HS as patients have more frequent interactions with nurses and general practitioners than with dermatologists or surgeons. For example, more detailed insights form patients into limitations in wound care, family care, personal hygiene or concomitant

diseases could have been generated by interviewing nurses, physicians or other informal care givers.

Both DCEs in HS were designed according to common recommendations and in collaboration with patient preference experts and experienced dermatologists(14,17,18). While the recruited samples were overall well-balanced, they had lower representation of black/African American participants than reported in epidemiological studies(10). This is a limitation as African populations have been reported to have more severe forms of HS, lower QoL, and more comorbid conditions, which would have potentially led to more diverse DCE findings(19). As DCEs have the inherent limitation that respondents are stating their preferences on hypothetical treatments, which may differ from real-life decision-making, both DCEs included dominance tests to improve their validity by excluding participants who preferred the dominated treatment option(20,21). As more treatments are becoming available in HS, future DCEs including real-life treatment choices could make the participants fill in the survey based on real-life experiences and maybe reduce the common limitation of stating treatment choices on purely hypothetical treatment options.

The economic evaluation in AtD intended to combine the advantages of previously published models(6). However, the final model structure still could not allow patients to switch between different levels of response health states and assumed that a patient is a non-responder if response to a particular level was lost. In reality, patients may however experience a tapering of response before completely losing response, but the health and cost consequences of this response tapering could not be accounted for. Furthermore, in the absence of resource use data of different response levels, these were conservatively assumed to be equal across different levels of response, which may have underestimated the healthcare cost benefits of the interventions allowing patients to achieve higher levels of response.

8.4. Implications and recommendations for future research

The SLR in PSO provided numerous recommendations to strengthen the validity of future preference research based on the limitations identified of included DCEs(1). Future DCEs were recommended to increase transparency on non-responders, to consider interviewer-led administration of DCEs to improve a respondent's comprehension of the exercise, to justify in more detail the experimental design chosen and to perform more frequent pilot-testing of the survey. As novel treatments in PSO become more effective which allows patients to achieve full

skin clearance, this treatment attribute could also be valuable to be explored in future preference research. Lastly, analysing the preferences of subgroups more systematically allows a better understanding of distinct preferences of particular groups and enables individualization of disease management according to their individual preferences.

While developing and reporting the results of the 'de novo' early economic evaluation for a treatment candidate in HS, numerous future research opportunities were outlined(5). Across all published economic evaluations of HS treatments reviewed for this study, treatment discontinuation rates and long-term benefits were consistently appraised to be one of the most important drivers of cost-effectiveness which highlights the importance to generate high quality evidence on maintenance of efficacy and treatment continuation for future treatment candidates in HS. In order to allow more certain reimbursement decision-making of HS treatment candidates, future research should generate clinical efficacy, quality of life, and economic data across a broader range of response levels. This will allow a more realistic simulation of the patient pathway as well as a better replication and validation of cost-effectiveness results.

The semi-structured interviews in HS confirmed the importance of qualitative research prior to designing quantitative preference elicitation studies due to the familiarization with the target population, their perceived unmet care needs and relevant treatment attributes(2). Assessing the trade-offs and relative importance of treatment attributes in larger samples using quantitative methods like DCEs was concluded to be promising to improve future clinical, regulatory, and reimbursement decision-making. The prioritization exercise of elicited treatment attributes allowed the identification of potential treatment attributes for inclusion in future DCEs. Furthermore, the study also cautioned about wider contextual circumstances in the HS care trajectory such as delays in diagnosis, access to specialists, and wound care issues which warrant consideration in the design of future quantitative preference studies.

The findings of both DCEs consistently suggested future development-, regulatory- and reimbursement decision-making to focus on offering HS treatments with higher levels of effectiveness that address patients' frequent complaints about lacking pain control(3,4). Future preference research with HS patients in other geographies, or with physicians was assessed to be promising to create a broader understanding of treatment preferences in HS. Furthermore, changing the treatment attributes or levels in DCE questionnaires to include e.g., cost of treatment, could reveal novel insights on the treatment considerations by patients with HS. Ultimately, the clinical

development and policy decision-making in HS should strive towards making a variety of treatment options available to enable individualized disease management according to patients' unique preferences.

The economic evaluation in AtD formulated recommendations for data generation of AtD treatments to focus on long-term treatment response and compliance to reduce uncertainty in future economic evaluations(6). As multiple options to model the patient pathway in AtD have been reported, future economic evaluations should consult patient and clinical expert opinion to address uncertainties on structural model parameters and assumptions. Furthermore, generating more robust clinical, cost and quality of life data across different response levels in AtD allows future economic evaluations to simulate the cost-effectiveness of therapies more accurately due to greater external validation opportunities.

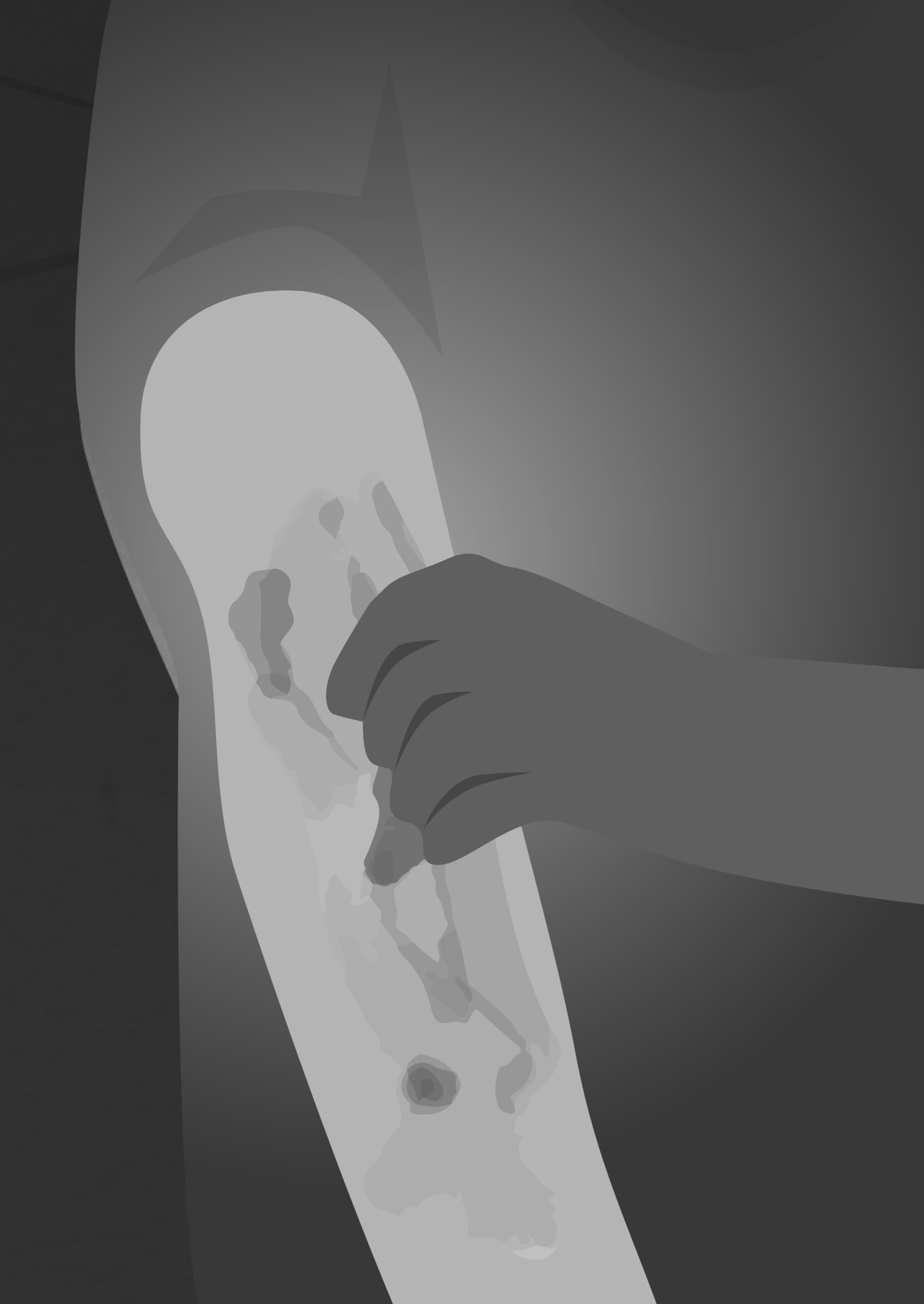
8.5. Conclusions

The research of this dissertation provided insights on the unmet care needs, treatment preferences and health economic implication in the field of chronic inflammatory skin diseases. It systematically evaluated the preferences of patients and physicians in published DCEs in PSO, provided qualitative insights on the unmet care needs and preferences from patients and physicians in HS which was followed by two quantitative preferences studies in the form of DCEs with HS patients in Europe and the US. In addition, two economic evaluations in HS and AtD explored under which circumstances treatment candidates can be considered cost-effective to allow future reimbursement. Furthermore, the presented research provided critical appraisals of the applied methodologies and highlighted promising opportunities for future research aiming to improve the outcomes of chronic inflammatory skin disease management.

8.6. References

1. Sain N, Willems D, Charokopou M, Hiligsmann M. The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments. Curr Med Res Opin 2020;36:1257-1275.
2. Willems D, Hiligsmann M, van der Zee HH, Sayed CJ, Evers S. Identifying Unmet Care Needs and Important Treatment Attributes in the Management of Hidradenitis Suppurativa: A Qualitative Interview Study. Patient 2022;15:207-218.
3. Willems D, Sayed CJ, Van der Zee HH et al. A discrete-choice experiment to elicit the treatment preferences of patients with hidradenitis suppurativa in the United States. J Med Econ 2023:1-9.
4. Willems D, Hinzpeter EL, Van der Zee HH et al. Patient Preferences in the Management of Hidradenitis Suppurativa: Results of a Multinational Discrete Choice Experiment in Europe. Patient 2023.
5. Willems D, Charokopou M, Evers S, Hiligsmann M. Early health economic modelling for a treatment candidate in hidradenitis suppurativa. J Med Econ 2020;23:1516-1524.
6. Heinz KC, Willems D, Hiligsmann M. Economic evaluation of a JAK inhibitor compared to a monoclonal antibody for treatment of moderate-to-severe atopic dermatitis from a UK perspective. J Med Econ 2022;25:491-502.
7. Florek AG, Wang CJ, Armstrong AW. Treatment preferences and treatment satisfaction among psoriasis patients: a systematic review. Arch Dermatol Res 2018;310:271-319.
8. Gonzalez JM. Evaluating Risk Tolerance from a Systematic Review of Preferences: The Case of Patients with Psoriasis. Patient 2018;11:285-300.
9. 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;82:366-376.
10. Garg A, Naik HB, Alavi A et al. Real-World Findings on the Characteristics and Treatment Exposures of Patients with Hidradenitis Suppurativa from US Claims Data. Dermatol Ther (Heidelb) 2022.
11. Ingram JR, Bettoli V, Espy JI et al. Unmet clinical needs and burden of disease in hidradenitis suppurativa: real-world experience from EU5 and US. J Eur Acad Dermatol Venereol 2022.
12. Faverio K, Peitsch WK, Gorig T et al. Patient Preferences in Hidradenitis Suppurativa (APProach-HS): a discrete choice experiment. J Dtsch Dermatol Ges 2022;20:1441-1452.
13. Joy SM, Little E, Maruthur NM, Purnell TS, Bridges JF. Patient preferences for the treatment of type 2 diabetes: a scoping review. Pharmacoeconomics 2013;31:877-92.
14. Bridges JF, Hauber AB, Marshall D et al. Conjoint analysis applications in health--a checklist: a report of the ISPOR Good Research Practices for Conjoint Analysis Task Force. Value Health 2011;14:403-13.
15. Tappenden P, Carroll C, Stevens JW et al. Adalimumab for Treating Moderate-to-Severe Hidradenitis Suppurativa: An Evidence Review Group Perspective of a NICE Single Technology Appraisal. Pharmacoeconomics 2017;35:805-815.
16. Somers C, Chimonas S, McIntosh E, Kaltenboeck A, Briggs A, Bach P. Using Nominal Group Technique to Identify Key Attributes of Oncology Treatments for a Discrete Choice Experiment. MDM Policy Pract 2019;4:2381468319837925.

17. Reed Johnson F, Lancsar E, Marshall D et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health 2013;16:3-13.
18. Lancsar E, Louviere J. Conducting discrete choice experiments to inform healthcare decision making: a user's guide. Pharmacoeconomics 2008;26:661-77.
19. Lee DE, Clark AK, Shi VY. Hidradenitis Suppurativa: Disease Burden and Etiology in Skin of Color. Dermatology 2017;233:456-461.
20. Laba TL, Brien JA, Fransen M, Jan S. Patient preferences for adherence to treatment for osteoarthritis: the MEdication Decisions in Osteoarthritis Study (MEDOS). BMC Musculoskelet Disord 2013;14:160.
21. Tervonen T, Schmidt-Ott T, Marsh K, Bridges JFP, Quaife M, Janssen E. Assessing Rationality in Discrete Choice Experiments in Health: An Investigation into the Use of Dominance Tests. Value Health 2018;21:1192-1197.



Summary

Summary

This dissertation identified the unmet care needs, treatment preferences and health economic implications in the field of chronic inflammatory skin diseases to optimize disease management outcomes.

In **chapter 2**, a systematic literature review of discrete choice experiments (DCE) in psoriasis (PSO) was conducted, which included 25 articles reporting patients' and physicians' preferences in treatment decision-making. Efficacy-related treatment outcomes were most important, and safety was frequently the second most important treatment attribute. Furthermore, PSO patients were found to place greater importance on process-related attributes than physicians. Age, disease severity, and duration of condition significantly affected preferences for treatment attributes in PSO.

Chapter 3 provided the results of a 'de novo' early cost-effectiveness model developed to assess the cost-effectiveness of a treatment candidate in hidradenitis suppurativa (HS). The base case results revealed the treatment candidate not to be cost-effective, but extensive scenario- and threshold analyses highlighted that reducing dosing or drug price improved the cost-effectiveness of the candidate. Cost-effectiveness was most sensitive to health states' utility values, treatment discontinuation, and resource utilization assumptions.

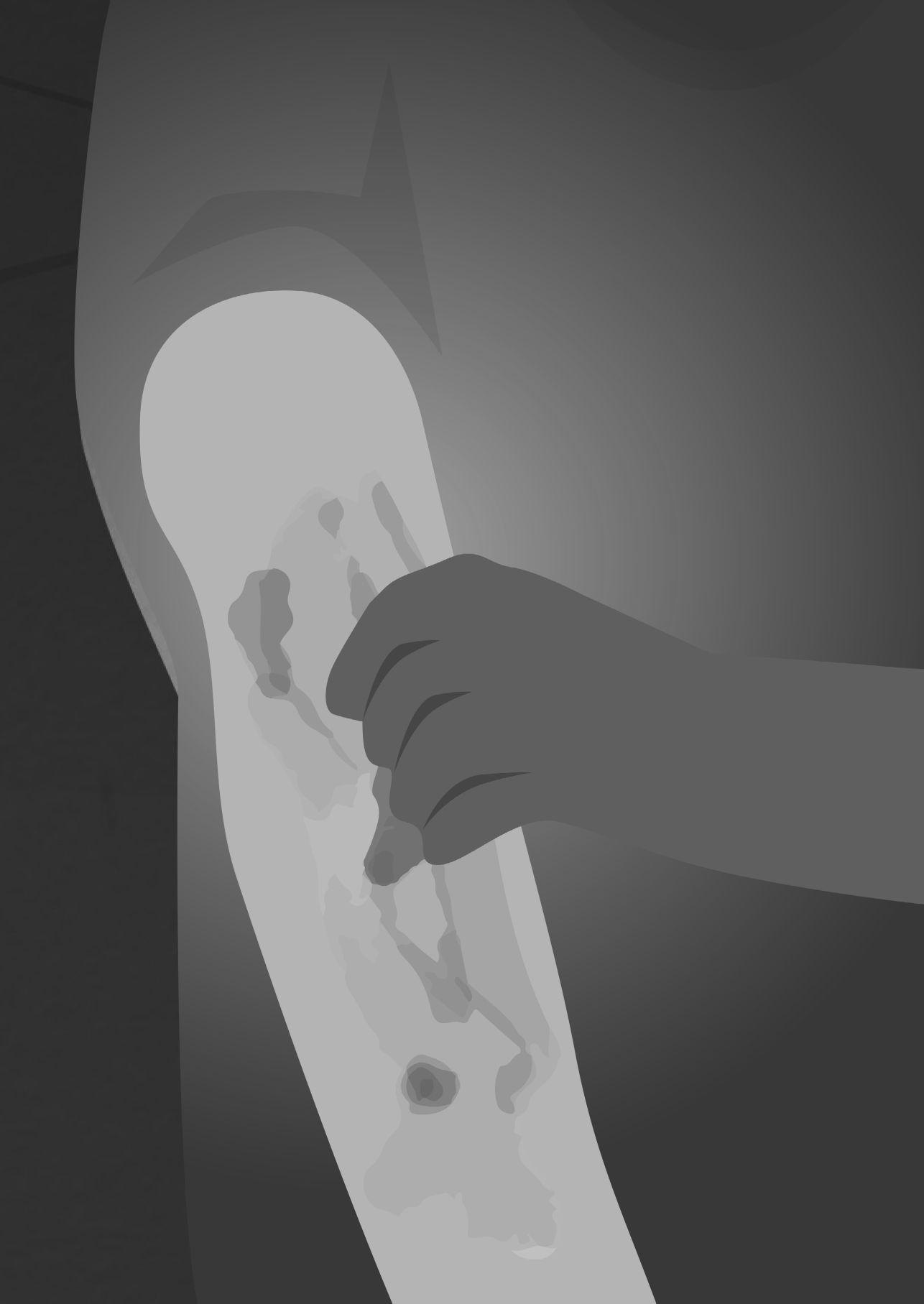
The semi-structured interviews with twelve HS patients and sixteen physicians presented in **chapter 4** revealed in total sixteen areas of unmet care needs and thirteen relevant treatment attributes. The most frequently reported unmet care needs were insufficient quality-of-life improvements, lacking treatment effectiveness, insufficient pain control, poor disease awareness, and delayed diagnosis. Patients reported unique concerns relating to pain control, access to dermatologists, and guidance on wound care.

The DCE across multiple countries in Europe detailed in **chapter 5** included 239 patients with HS. The most important treatment attributes to patients with HS were effectiveness, followed by pain reduction. For all six treatment attributes included, significant differences were observed between levels which indicated the included attributes were relevant for respondents. Higher levels of effectiveness, namely a 75% or 100% reduction in the abscess and inflammatory nodule count, were preferred over lower levels of effectiveness (e.g., 50% reduction). The finding of this DCE were consistent across subgroups.

A similar DCE with 100 HS patients in the US, as presented **in chapter 6**, confirmed the most important treatment attributes to be effectiveness and pain reduction.

The 'de novo' cost-effectiveness model in AtD was developed to assess the cost-effectiveness of a novel JAK inhibitor compared to a monoclonal antibody for the treatment of moderate-to-severe AtD in the United Kingdom and to identify key drivers of cost-effectiveness. By reporting the cost-effectiveness results alongside opportunities for future clinical-, cost- and quality of life evidence generation allowed this study presented in **chapter 7** contributed to increase reimbursement chances of investigational therapies in AtD.

The research of this dissemination presented a robust synthesis of patient preference evidence in PSO, generated unprecedent qualitative and quantitative patient-centric research in HS and explored the economic viability of two treatment candidates in HS and AtD which allows future health policy-making to relief patients, physicians and society from the high burden of these diseases by improving disease management options according to patients and physicians' preferences.



Impact

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Main objective and main results

This dissertation explored the unmet care needs, treatments preferences and health economic implications in the field of chronic inflammatory skin disorders. The unmet care needs and preferences of patients and physicians in psoriasis were revealed to not be adequately addressed by available treatments options according to a systematic literature review conducted(1). The considerable differences of preferences in psoriasis highlighted the importance to make more diverse interventions available to allow individualization of patient care and improve disease management outcomes (chapter 2). In hidradenitis suppurativa, the limited published patient-centric research motivated the generation of novel insights on the unmet care needs and treatment preferences from the perspectives of patients and physicians in chapter 4(2). Important differences in perceptions of unmet care needs and treatment preferences were identified between patients and physicians and across geographies, possibly due to differences in care pathways or patient profiles (chapters 5 & 6). Unmet care needs and treatment preferences were revealed to be likely caused by low effectiveness of the few available treatment options which, leaving patients and physicians having to cope with uncontrolled flares, pain and disease progression(3,4). Two newly developed health economic models revealed under which health benefits and costs circumstances two treatment candidates for hidradenitis suppurativa and atopic dermatitis could be considered cost-effective to enable their future reimbursement to improve disease management outcomes in chapters 3 and 7(5,6).

Scientific impact

The systematic literature review on treatment preferences of patients with psoriasis and physicians confirmed findings of previous reviews reporting efficacy to be the most influential treatment attribute for both patients and physicians in psoriasis. Detailed quality assessments using established checklists allowed the formulation of recommendations to strengthen the methodology of future evidence syntheses studies in psoriasis. Developing and correctly interpreting the results of an early economic evaluation in hidradenitis suppurativa required a critical appraisal of existing economic evaluations in hidradenitis suppurativa(5). The findings of this research added value to existing evidence by estimating the possible economic value of a treatment candidate for hidradenitis suppurativa that had not been appraised before. Furthermore, by exploring key drivers of cost-effectiveness, suggestions on which evidence and price levels future treatments for hidradenitis

suppurativa should expect to achieve favourable cost-effectiveness outcomes for reimbursement could be formulated.

The qualitative research using semi-structured interviews with patients with hidradenitis suppurativa and physicians in Europe and North-America increased the currently insufficient understanding of the unmet care needs and provided evidence for complementary quantitative preference research(2). The findings confirmed previous research reporting high levels of unmet care needs with pain, physical signs and HS-specific QoL as most apparent domains(7-9).

The findings of the interview study hidradenitis suppurativa subsequently served as basis for the first multi-national discrete-choice experiment questionnaire with patients in Europe aiming to investigate the most important treatment attributes(4). A similar discrete-choice experiment with hidradenitis suppurativa patients in the United States was conducted to explore the transferability of findings across geographies. The treatment preferences between patients enrolled in different discrete-choice experiments in Europe, Germany and the US were similar with patients consistently emphasizing effectiveness and pain control as most important with safety outcomes being less important(3,4,10).

Using a 'de novo' developed cost-effectiveness model in atopic dermatitis, the cost-effectiveness of a Janus Kinase inhibitor was explored under UK settings. Furthermore, the novel model structure addressed the shortcomings of previous models by incorporating three instead of one response endpoint to allow a more precise and realistic simulation of health and cost consequences of included treatments.

Social impact

Health economics research informs policy-makers on the most efficient way to allocate the limited resources of a healthcare system. With policy-makers being payers, politicians, administrators, or clinicians, health economics has the potential to contribute to resource-efficient development-, regulatory- and reimbursement decisions to improve the disease management outcomes of chronic inflammatory skin diseases. In particular, designing future interventions that aim to address the unmet care needs and meet the preferences of patients may positively influence treatment satisfaction and adherence(11-13). The research of this dissemination presented a robust synthesis of available patient preference evidence in psoriasis, generated unprecedent qualitative and quantitative patient-centric research in hidradenitis suppurativa and explored the economic viability of two treatment candidates in hidradenitis suppurativa and atopic dermatitis. This research allows

future healthcare decision-making to reduce the very high burden of disease and unmet care needs with more successful treatment options that match patients and physicians' preferences.

Dissemination of research results

In addition to the publication of this dissemination, individual components of this thesis (chapters 2-7) were separately published in highly recognized peer-reviewed scientific journals(1-6). All manuscripts were published 'open access' to be accessible free of charge for patients, physicians and policy-makers. Each publication was further announced via social media channels to augment their awareness and impact.

References (Impact)

1. Sain N, Willems D, Charokopou M, Hiligsmann M. The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments. Curr Med Res Opin 2020;36:1257-1275.
2. Willems D, Hiligsmann M, van der Zee HH, Sayed CJ, Evers S. Identifying Unmet Care Needs and Important Treatment Attributes in the Management of Hidradenitis Suppurativa: A Qualitative Interview Study. Patient 2022;15:207-218.
3. Willems D, Sayed CJ, Van der Zee HH et al. A discrete-choice experiment to elicit the treatment preferences of patients with hidradenitis suppurativa in the United States. J Med Econ 2023:1-9.
4. Willems D, Hinzpeter EL, Van der Zee HH et al. Patient Preferences in the Management of Hidradenitis Suppurativa: Results of a Multinational Discrete Choice Experiment in Europe. Patient 2023.
5. Willems D, Charokopou M, Evers S, Hiligsmann M. Early health economic modelling for a treatment candidate in hidradenitis suppurativa. J Med Econ 2020;23:1516-1524.
6. Heinz KC, Willems D, Hiligsmann M. Economic evaluation of a JAK inhibitor compared to a monoclonal antibody for treatment of moderate-to-severe atopic dermatitis from a UK perspective. J Med Econ 2022;25:491-502.
7. Garg A, Naik HB, Alavi A et al. Real-World Findings on the Characteristics and Treatment Exposures of Patients with Hidradenitis Suppurativa from US Claims Data. Dermatol Ther (Heidelb) 2022.
8. Ingram JR, Bettoli V, Espy JI et al. Unmet clinical needs and burden of disease in hidradenitis suppurativa: real-world experience from EU5 and US. J Eur Acad Dermatol Venereol 2022.
9. 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;82:366-376.
10. Faverio K, Peitsch WK, Gorig T et al. Patient Preferences in Hidradenitis Suppurativa (APProach-HS): a discrete choice experiment. J Dtsch Dermatol Ges 2022;20:1441-1452.
11. Umar N, Schaarschmidt M, Schmieder A, Peitsch WK, Schollgen I, Terris DD. Matching physicians' treatment recommendations to patients' treatment preferences is associated with improvement in treatment satisfaction. J Eur Acad Dermatol Venereol 2013;27:763-70.
12. Jevtic T, Bukumiric Z, Jankovic SM. Effects of treatment adherence on clinical and economic outcomes in patients with psoriasis. Med Glas (Zenica) 2013;10:106-12.
13. Gaspar K, Hunor Gergely L, Jenei B et al. Resource utilization, work productivity and costs in patients with hidradenitis suppurativa: a cost-of-illness study. Expert Rev Pharmacoecon Outcomes Res 2021:1-10.

Dissemination activities

Dissemination activities

Scientific Articles in Peer-Reviewed Journals

Sain, N., Willems, D., Charokopou, M., & Hiligsmann, M. (2020). The importance of understanding patient and physician preferences for psoriasis treatment characteristics: a systematic review of discrete-choice experiments. *Current Medical Research and Opinion*, *36*(8), 1257-1275.

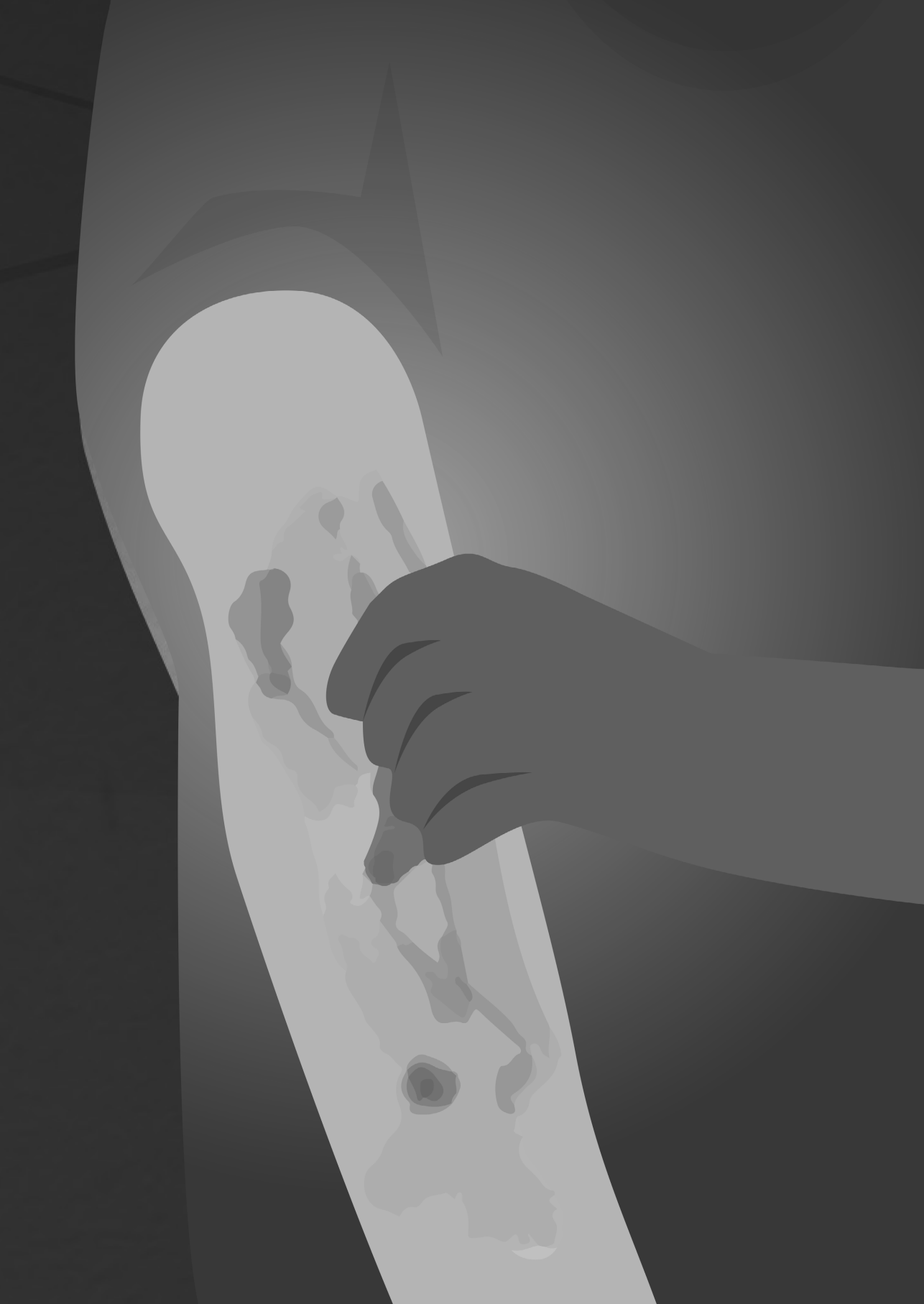
Willems, D., Charokopou, M., Evers, S. M., & Hiligsmann, M. (2020). Early health economic modelling for a treatment candidate in hidradenitis suppurativa. *Journal of Medical Economics*, *23*(12), 1516-1524.

Willems, D., Hiligsmann, M., van der Zee, H. H., Sayed, C. J., & Evers, S. M. (2021). Identifying unmet care needs and important treatment attributes in the management of hidradenitis suppurativa: a qualitative interview study. *The Patient-Patient-Centered Outcomes Research*, 1-12.

Willems, D., Hinzpeter, E. L., Van der Zee, H. H., Sayed, C. J., Ingram, J. R., Beaudart, C., Evers, S., & Hiligsmann, M. (2023). Patient Preferences in the Management of Hidradenitis Suppurativa: Results of a Multinational Discrete Choice Experiment in Europe. *The Patient-Patient-Centered Outcomes Research*, 16(2), 153-164.

Willems, D., Sayed, C. J., Van der Zee, H. H., Ingram, J. R., Hinzpeter, E., Beaudart, C., Evers, S., & Hiligsmann, M. (2023). A discrete-choice experiment to elicit the treatment preferences of patients with hidradenitis suppurativa in the United States. *Journal of Medical Economics*, 26(1), 503-508.

Heinz, K. C., Willems, D., & Hiligsmann, M. (2022). Economic evaluation of a JAK inhibitor compared to a monoclonal antibody for treatment of moderate-to-severe atopic dermatitis from a UK perspective. *Journal of Medical Economics*, *25*(1), 491-502.



About the author

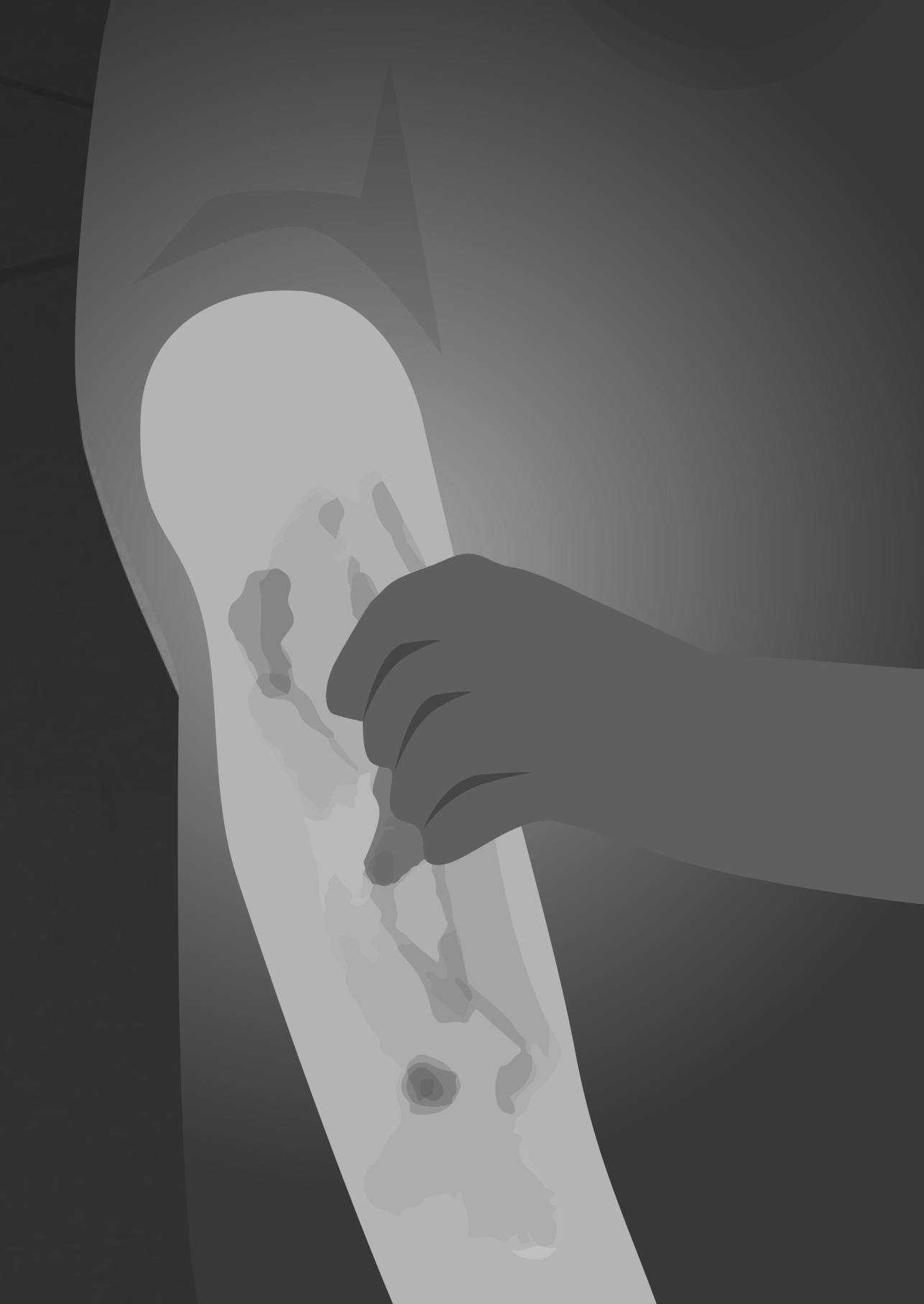
About the author

Damon Willems was born on 6th September of 1995 in Eupen, Belgium. After receiving his B.Sc. degree in European Public Health at Maastricht University in 2016, he continued his studies at the University of Cologne to obtain his first M.Sc. degree in Health Economics before returning to Maastricht University to obtain his second M.Sc. degree in Healthcare Policy, Innovation and Management.

Following an internship focusing on Health Technology Assessments at UCB Pharma, Damon started working as Global Health Economics Lead at UCB Pharma in 2018 and transitioned into the role of EU Market Access Lead in 2022. Throughout his occupation at UCB Pharma, Damon led the development and implementation of cost-effectiveness- and budget-impact models, network meta-analyses and real-world evidence projects in the field of Immunology that supported UCB to achieve reimbursement of its therapeutic solutions. In parallel to his occupation at UCB, Damon was an external PhD student at the Department of Health Services Research of Maastricht University between 2019 and 2024.

Damon has over 5 years of experience in market access, outcomes research and health economics in the pharmaceutical industry. He is very passionate about sharing his expertise and ideas with colleagues and scientific communities and therefore has been a guest lecturer at Maastricht University on Health Technology Assessments and is very committed to make his research publicly available through scientific publications. He also supervised multiple M.Sc. intern students from Maastricht University in the Market Access Team at UCB Pharma and regularly attends university career events to help students succeed with their first professional occupations after graduation.

In his private life, Damon enjoys a variety of different sports and outdoor activities, in particular football, squash and tennis but also enjoys relaxing moments with his close friends and family including Labradoodle ‘Leni’.



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