UNIVERSIDADE D
COIMBRA

Ana Isabel Noronha Sousa

Relatórios de Estágio sob a orientação da Dra. Mariana Noronha e Dra. Dina Lopes e Monografia intitulada "Characterization of the pharmacotherapeutic evaluation processes of medicines used in the treatment of Inflammatory Bowel Diseases" sob orientação do Professor Doutor Carlos Alves, referentes à Unidade Curricular "Estágio", apresentados à Faculdade de Farmácia da Universidade de Coimbra, para apreciação na prestação de provas públicas de Mestrado Integrado em Ciência Farmacêuticas.

Setembro de 2023

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Setembro 2023

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Coimbra, 6 de setembro de 2023

Ana Isabel Noronha Sousa

(Ana Isabel Noronha Sousa)

Agradecimentos

Com o encerrar desta etapa, e início de um novo começo, quero agradecer a todas as pessoas que durante todo o meu percurso académico me acompanharam e contribuíram para o meu sucesso.

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Por fim, gostava de dedicar a minha tese, que representa o culminar do meu percurso académico à minha Avó.
"Não estás cá, mas para ti é."

O meu mais sincero obrigada!

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"Characterization of the pharmacotherapeutic evaluation processes of medicines used on the treatment of Inflammatory Bowel Diseases."

PARTE I

RELATÓRIO DE ESTÁGIO EM FARMÁCIA COMUNITÁRIA

Farmácia Miranda – Lisboa

Lista de Abreviaturas

ANF - Associação nacional das farmácias

DT - Diretora técnica

FFUC - Faculdade de farmácia da universidade de Coimbra

INFARMED, I.P. - Autoridade nacional do medicamento e produtos de saúde I.P.

MICF - Mestrado integrado em ciências farmacêuticas

MNSRM - Medicamentos não sujeitos a receita médica

SWOT - *Strengths, Weaknesses, Opportunities, Threats*

1 Introdução

De acordo com o disposto no Código Deontológico da Ordem dos Farmacêuticos, o farmacêutico tem como principal dever contribuir para a saúde e o bem-estar da pessoa em geral, e em particular, no contexto da saúde, devendo pôr o bem dos indivíduos à frente dos seus interesses pessoais ou comerciais[1]. Desde cedo, esta é uma premissa que é nos é incutida ao longo do percurso académico aos estudantes de Mestrado Integrado em Ciências Farmacêuticas (MICF), ministrado na Faculdade Farmácia da Universidade de Coimbra (FFUC).

Ao longo dos 5 anos, que constituíram a minha formação académica, pude desenvolver o meu sentido de responsabilidade para com o próximo e a par, construir com a ajuda de toda a equipa docente, os alicerces teóricos necessários para exercer a minha futura profissão com o maior rigor e excelência.

A FFUC elaborou um plano curricular, que nos permite enquanto estudantes, completar a nossa formação teórica com uma vertente prática. Neste sentido, o Estágio Curricular surge, com conotação de Unidade Curricular, de forma a permitir os estudantes aplicarem todo o conhecimento científico, bem como desenvolver as competências práticas, colmatando possíveis falhas nas competências técnicas e interpessoais essenciais para nós, estudantes e futuros farmacêuticos, desempenharmos a nossa profissão com o maior rigor e autonomia.

Neste âmbito, culmino os meus 5 anos de estudos, com um estágio na Farmácia Miranda, na cidade de Lisboa, sob a orientação da Dra. Mariana Noronha enquanto Diretora Técnica (DT). O presente relatório versa sobre esta experiência, que teve início no dia nove de janeiro de 2023 e findou no dia vinte e oito de abril do mesmo ano. Esta é indiscutivelmente uma das etapas mais enriquecedoras do MICF, constituindo na minha perspetiva, a interface entre todo o trajeto académico e o trajeto profissional.

2 Análise SWOT

Redigi o presente relatório de uma forma retrospetiva e seguindo um modelo de análise SWOT *(Strenghts, Weaknesses, Opportunities, Threats)*, onde pretendo analisar de uma perspetiva interna, as "Forças" e "Fraquezas" inerentes ao processo da minha formação, e numa perspetiva externa, as "Oportunidades" e "Ameaças" sentidas durante este processo.

2.1 Pontos Fortes

2.1.1 Acolhimento e integração na equipa

Do meu ponto de vista são diversos os fatores que podem contribuir para o bom funcionamento de uma farmácia, mas sem dúvida a sua equipa é o mais preponderante. No

que diz respeito à equipa da Farmácia Miranda, esta não se cinge a ser simplesmente colegas, mais sim amigos. Esta é uma equipa que considero ideal para qualquer empresa, equilibrada, focada e motivada, não só no bom funcionamento da farmácia, mas também no utente.

Sem dúvida, as pessoas com quem trabalhei fizeram toda a diferença, para aquilo que considero ter sido um estágio bem-sucedido. Logo desde início, a simpatia e empatia cativaram a minha vontade de aprender, bem como a disponibilidade de todas a colaboradoras, para me ensinar, orientar e apoiar.

Dentro da farmácia, existe um mapa de tarefas mensais que promove a organização e bom funcionamento da mesma. Durante os 4 meses que constituíram o meu estágio, pude rodar por todas as tarefas desempenhadas por cada colaboradora, permitindo-me ter uma noção geral de como se processa o trabalho dentro de uma farmácia.

As colaboradoras da Farmácia Miranda destacam-se pelo seu profissionalismo e disponibilidade em ensinar-me todas as competências necessárias para desempenhar um trabalho de qualidade, não só do ponto de vista técnico, mas também do ponto de vista social, estimulando o desenvolvimento de aptidões ao nível da comunicação, que promoveram as minhas relações com os utentes. Adicionalmente, deste cedo impulsionaram o meu espírito crítico, equilibrando a autonomia com o apoio, permitindo-me relembrar e apurar conteúdos lecionados ao longo do plano de estudo de MICF.

2.1.2 Sifarma2000®

A Farmácia Miranda tal como a grande maioria das farmácias a nível nacional, opera com o Sifarma2000®, como *software* eleito para efetuar toda a gestão da farmácia na parte do *backoffice,* e no atendimento opera com o novo Módulo de Atendimento do Sifarma, um *software* relativamente novo que têm vindo a ser cada vez mais introduzido nas farmácias. Com o decorrer do estágio, pude perceber a importância de conseguir operar este sistema operativo, uma vez que está presente na maior parte das tarefas desempenhadas, desde o *back office* ao atendimento.

Apesar de já ter contactado anteriormente com este *software,* oportunidade que nos foi dada no decorrer das aulas de Organização e Gestão Farmacêutica, este contacto foi muito breve, por isso com o decorrer do estágio pude aperfeiçoar os meus conhecimentos acerca do manuseamento do Sifarma, algo que considero extremamente importante caso no futuro queira enveredar pelo caminho da Farmácia Comunitária, uma vez que este é o sistema informático mais utilizado em Portugal.

2.1.3 Dermofarmácia e Cosmética

O mundo da dermofarmácia e cosmética, antes de iniciar o meu estágio, era sem dúvida a área com a qual estava menos à vontade. O plano de estudos de MICF, contempla a unidade curricular de Dermofarmácia e Cosmética, cadeira esta, muito bem estruturada e completa, o que sem dúvida colocou-me em vantagem quando iniciei o meu estágio. No entanto, o mundo da cosmética é tão vasto o que torna inevitável o nervosismo associado a este tipo de aconselhamento numa fase inicial.

Contudo, a secção de dermofarmácia e cosmética da Farmácia Miranda é uma secção extensamente desenvolvida e trabalhada, contendo desde diferentes marcas, a diversas gamas que abrangem um vasto leque de faixas etárias. A elevada diversidade de produtos desta secção, permitiu-me alargar o meu conhecimento nesta área que acho tão atual e fundamental numa farmácia. Tive oportunidade de apurar o meu atendimento personalizado aos utentes, além de compreender como aconselhá-los de forma a otimizar e promover a utilização de produtos cosméticos.

2.1.4 Serviços Farmacêuticos

Os serviços farmacêuticos disponibilizados na Farmácia Miranda englobam desde medição de parâmetros bioquímicos como, a glicémia, colesterol e triglicéridos à medição da pressão arterial, e ainda vacinação. Numa primeira instância tive oportunidade de obter formação acerca dos serviços acima referidos, nomeadamente acerca da sua correta execução, mas também sobre como comunicar e interagir de forma adequada com os utentes.

Tive ainda o privilégio de poder assistir à administração de duas soluções injetáveis em canetas pré-cheias, Trulicity® e Ozempic®, em dois utentes que se deslocavam com regularidade à farmácia para obter ajuda neste tipo de administração.

Considero a disponibilização deste tipo de serviços de extrema importância, uma vez que promove o aconselhamento e aproximação ao utente, bem como possibilita desenvolver relações de confiança, que na minha opinião são a base de qualquer relação farmacêutico-utente.

No que toca à minha experiência de estágio, considerei que foi um ponto forte, pois possibilitou-me criar laços com os utentes e desenvolver a minha capacidade de comunicação com os mesmos.

2.2 Pontos Fracos

2.2.1 Preparação de Medicamentos Manipulados

Um medicamento manipulado, é todo e qualquer preparado oficinal (medicamento preparado de acordo com as indicações expressas na Farmacopeia ou Formulário) ou fórmula magistral (medicamento preparado exclusivamente para um utente e de acordo com uma receita médica) que é preparado e dispensado sob a inteira responsabilidade de uma farmacêutica[2]. Este preparado segue obrigatoriamente um elevado padrão de qualidade que é definido pela Portaria n.º 594/2004, de 2 de Junho, onde se aprovou as "boas práticas a observar na preparação de medicamentos e manipulados".

Estes são produtos essenciais em situações em que medicação prescrita tem de ser adaptada e ir completamente de encontro às necessidades do utente, em situações de inexistência de opções terapêuticas que compreendam estes requisitos.

Durante o meu estágio na Farmácia Miranda, não tive a oportunidade de executar este tipo de preparação uma vez que a farmácia não dispunha deste serviço. Considero ter sido um ponto fraco do meu estágio, pois não contactando com este serviço não tive oportunidade de conhecer esta que é uma das vertentes da Farmácia Comunitária, colocando-me em desvantagem para com os meu colegas que puderam aperfeiçoar estas competências.

2.3 Oportunidades

2.3.1 Reunião com Delegado Comercial

Durante o meu estágio, a Dra. Mariana Noronha, concedeu-me a oportunidade de poder assistir a uma das várias reuniões que tem ao longo dos meses com os delegados comerciais dos laboratórios. Nestas reuniões, normalmente abordam-se diversos assuntos como apresentação das campanhas para os próximos meses, apresentação de novas marcas ou novos produtos, agendamento de possíveis formações disponibilizadas às farmácias, contextualização do *sell-out* relativo aos produtos comprados no trimestre ou ano anterior, análise de vendas dos períodos homólogos e por fim, e mais importante, efetuar a compra de produtos para os próximos meses e respetiva entrega dos mesmos.

Antes da reunião, a Dra. Mariana contextualizou-me relativamente ao laboratório com que íamos reunir, bem como os produtos que já tínhamos no portefólio da farmácia. Explicou-me ainda todo o processo de preparação da reunião e o pós-reunião, que inclui retirar e analisar a listagem de vendas dos produtos em questão e ainda posteriormente discussão e

planeamento de dinamização da farmácia de modo a promover a venda dos produtos comprados.

Considero que esta foi uma oportunidade única, de poder perceber e aprender como se processam estas negociações entre as farmácias e laboratórios, bem como a dinâmica das mesmas. Consegui adquirir também uma pequena noção daquilo que é a gestão de uma farmácia para além do atendimento e *backoffice*.

2.3.2 Formações sobre as marcas

Nos dias de hoje, a farmácia não é vista apenas como um local de compra de medicamentos, mas como um local de procura de aconselhamento relativamente não só aos medicamentos sujeitos a receita médica, mas também aos medicamentos não sujeitos a receita médica (MNSRM), cosmética e dispositivos médicos.

A Farmácia Miranda contempla um portefólio enorme de diferentes produtos e diferentes marcas. Nos dias de hoje, mais importante que saber comprar bem, é saber vender bem e, para isso, é necessária uma compreensão profunda acerca dos produtos e do seu modo de utilização. Para isso, os laboratórios disponibilizam-se para dar formação aos farmacêuticos e técnicos sobre os produtos e a retirar possíveis dúvidas que possam ter surgido aquando da venda dos mesmos, quer no espaço da farmácia quer em sessões organizadas em hotel.

Durante os quatro meses que contemplaram o meu estágio, pude assistir a duas formações que decorreram na farmácia, uma sobre pensos rápidos da Hartmann e outra sobre escovas de dentes da Elgydium®. A par destas, pude ainda deslocar-me à sede da SVR e Lazartige® para participar numa formação intensiva, que durou um dia, em que apresentaram novos produtos da marca e ainda reforçaram o conhecimento acercas dos mais antigos.

Considero que estas foram oportunidades extremamente importantes, pois pude conhecer, aprender e reforçar o meu aconselhamento sobre os produtos apresentados, o que contribuiu para um aumento do meu desempenho ao balcão.

2.4 Ameaças

2.4.1 Sazonalidade

A realização do meu estágio coincidiu com os meses de inverno e início de primavera, compreendendo o período de janeiro a abril. Posto isto, as necessidades dos utentes, bem como o aconselhamento prestado foram muito de encontro ao tipo de produtos dispensado em casos de constipação, gripe, congestão nasal, alergias e distúrbios ocasionais gastrointestinais.

Considero que desta forma, não tive oportunidade de trabalhar outro tipo de produtos normalmente associados à estação do verão e outono, o que limitou em parte a minha aquisição de conhecimento, podendo constituir uma ameaça, para a minha futura entrada no mercado de trabalho.

2.4.2 Medicamentos esgotados e rateados

Medicamentos esgotados e rateados, são uma realidade atual das farmácias em Portugal, realidade esta à qual a Farmácia Miranda não foi exceção à regra. A lista de medicamentos esgotados é extensa e não olha ao facto de se tratar de marca ou genérico, sendo que muitas foram as vezes em que um utente se dirigiu à farmácia para levantar a sua receita e por consequência via impossibilitado o início do seu plano terapêutico.

A origem por de trás deste problema, não é clara e pode ser variada, muitas vezes pode dever-se a problemas na produção outra vezes devido ao excesso de exportações paralelas. Facto é, que a resolução deste problema, é alheia ao farmacêutico comunitário, sendo que este acaba por enfrentar o problema perante os utentes que são os principais lesados. Além do mais, este problema, obriga a uma otimização de *stocks* bem como a criação de listas de espera para estes medicamentos.

Esta condicionante impactou em muito a minha experiência no atendimento, sendo que tive que aprender a lidar com a agitação do utente face a esta falta de medicamentos.

2.4.3 Desconfiança nos medicamentos Genéricos

Apesar de todos os esforços já feitos na consciencialização da população por parte dos farmacêuticos, Autoridade Nacional do Medicamento e Produtos de Saúde I.P. (INFARMED, I.P.) e Associação Nacional da Farmácias (ANF), os medicamentos genéricos continuam a ser alvo de desconfiança na população em geral, a nível da sua eficácia e segurança. Tal aversão, é muitas vezes justificada pelo seu baixo preço que intuitivamente é associado à diminuição de qualidade e eficácia face ao correspondente medicamento de marca. Muitas foram as vezes em que me defrontei com resistência na compra de genéricos, e por vezes até recusa, mesmo não havendo outra opção disponível.

Considero que as razões deste ceticismo devem ser bem esclarecidas e reforçados os esforços na consciencialização da população de forma a reduzir o preconceito associado aos medicamentos genéricos.

3 Casos Práticos

Caso Prático 1 - Candidíase vaginal

Utente do sexo feminino com cerca de 30 anos, deslocou-se à farmácia queixando-se de prurido intenso na zona vulvar e aparecimento de um corrimento esbranquiçado espesso e sem odor notório.

Face aos sintomas descritos, percebi que se poderia tratar de um caso de candidíase vaginal, uma infeção fúngica normalmente provocada pela espécie *Candida* albicans, e que ocorre com mais frequência em utentes adultas com idade entre os 16 e 60 anos. Rapidamente questionei se é recorrente a senhora ter este tipo de sintomas e se já tinha tomado algum medicamento para atenuar os mesmos. A senhora indicou, que costuma experienciar este tipo de sintomas cerca de duas vezes por ano e afirmou que ainda não tinha tomado nada.

De forma a complementar o meu diagnóstico, questionei se estava a fazer algum contracetivo oral, imunossupressores, terapêutica hormonal de substituição ou se tinha feito recentemente algum tipo de antibiótico. A senhora afirmou que já tomava contracetivos orais há cerca de 10 anos, mas que não fez outro tipo de medicação para além desta.

Após o diagnóstico, expliquei sucintamente a possível origem por de trás dos seus sintomas e indiquei-lhe o antifúngico Gino-Canesten® (clotrimazol) 10 mg/g creme vaginal, explicando-lhe que deve utilizar a seringa para aplicar o creme mais profundamente na vagina, uma vez por dia ao deitar, por 6 dias consecutivos. Expliquei ainda, que apesar da candidíase vaginal não ser considerada uma doença sexualmente transmissível, as relações sexuais devem ser evitadas, ou utilizado preservativo durante o período de tratamento de forma a evitar a disseminação da infeção para o parceiro. Reforcei a importância de, aquando da ida à casa de banho, a limpeza da zona genital dever ser feita de frente para trás na direção do ânus e ainda recomendei a utilização de gel de limpeza ou sabão neutro no banho utilizando, por exemplo, o Lactacyd Pharma com Prebióticos®, que foi especialmente desenvolvido para mulheres com tendência para infeções vaginais. Por fim, aconselhei ainda algumas medidas não farmacológicas, como a utilização de cuecas de algodão e a troca das mesmas diariamente, evitando sempre a utilização de pensos higiénicos diários.

Em conclusão alertei para a monitorização dos sintomas que se persistissem após 7-14 dias, devia consultar um médico especialista.

Caso Prático 2 - Diarreia

Um utente do sexo masculino com cerca de 20 anos, deslocou-se ao balcão da farmácia referindo que estava com diarreia há dois dias e que necessitava de algo que aliviasse os

sintomas o mais rapidamente possível. Comecei por questionar ao senhor, se tinha experienciado febre, vómitos ou dores abdominais, se notou aparecimento de sangue, pus ou muco nas fezes ou se apresentava sinais de desidratação, como sede, boca seca, fadiga ou cefaleias. O senhor respondeu, que as suas fezes não apresentavam nada de anormal para além da consistência que era bastante líquida e que não experienciou febre. No entanto, afirmou que a sua urina se encontrava-se muito escura, e que realmente sentia muita sede. Adicionalmente. questionei se o senhor se encontrava a fazer algum tipo de medicação ou se tinha viajado recentemente, sendo que este respondeu negativamente a estas questões.

Assim procedi o atendimento, começando por aconselhar o Imodium Rapid® (lorapamida) 2 mg comprimido orodispersível, começando com uma dose inicial de 2 comprimidos, seguidos de 1 comprimido após cada nova dejeção, concomitantemente com a toma de Dioralyte® (eletrólitos + glucose) pó para solução oral, aconselhando a toma de 1 a 2 saquetas dissolvidas em 200 ml ou 400 ml respetivamente, após cada dejeção, de forma a repor os eletrólitos e combater a desidratação do senhor. Adicionalmente, sugeri a toma de Atyflor®, suplemento alimentar probiótico que iria ajudar a regular a flora intestinal, fazendo 1 por dia até uma consistência normal das fezes.

De forma a complementar o aconselhamento, aconselhei medidas não farmacológicas como fazer a abundante ingestão de líquidos como água ou chá fraco, de forma a repor os fluidos e eletrólitos, aconselhei para a ingestão de alimentos ricos em amidos, como arroz branco, massa e batata, evitando sempre os peixes e carnes gordas, produtos lácteos e bebidas com álcool.

Por fim, alertei o senhor para a monitorização dos sintomas, que se não melhorarem após 2 dias, devia deslocar-se ao médico.

Caso Prático 3 - Contraceção oral de emergência

Uma utente com cerca de 20 anos desloca-se à farmácia e pede a pílula do dia seguinte. Iniciei o meu atendimento, aproximando-me um pouco da senhora e baixando o meu tom de voz deixando-a confortável em falar sobre o assunto e comecei por perguntar há quanto tempo teve a relação sexual desprotegida, se foi há mais de 5 dias, e se teria tomado algum contracetivo oral de emergência (COE) durante o atual ciclo menstrual. A senhora respondeu afirmando que, a relação sexual teria sido no dia anterior e que nunca tinha recorrido a nenhum COE.

Prossegui, questionando se a utente tomava algum tipo de medicação regular ou se estaria a fazer alguma medicação no momento, à qual a resposta foi negativa. Desta forma, decidi

ceder à senhora o Postinor® 1500 microgramas (levonorgestrel) comprimido, aconselhando a que efetuasse a toma logo que possível, uma vez que ainda se encontrava dentro do período de maior eficácia (até as 72h) do COE. Adicionalmente, informei a senhora que a eficácia do COE é tanto maior quanto mais rapidamente for iniciado o tratamento, e que caso esteja a fazer algum contracetivo oral de uso regular, pode continuar a sua toma normal. Alertei que seria importante associar-se um método contracetivo de barreira até ao início da menstruação seguinte, que nos dias que se seguem pode experienciar alguns efeitos adversos como, náuseas, vómitos, tensão mamária, cefaleias, dor abdominal e alterações do ciclo menstrual.

Por fim, aconselhei que estivesse atenta à sua próxima menstruação que, devido à toma do COE, poderia ocorrer alguns dias antes ou depois, e que se tardasse mais de 5 a 7 dias deveria realizar um teste de gravidez.

Caso Prático 4 - Tosse com expetoração

Um senhor com cerca de 50 anos deslocou-se a farmácia com queixas de tosse intensa que já durava há uma semana, queixou-se ainda de alguma irritação na garganta. Comecei por questionar o senhor se teria experienciado algum episódio de febre e se a sua tosse apresentava expetoração ou não, e se sim qual era a sua aparência. Ao qual o senhor respondeu que sentiu febre na noite anterior e que efetivamente estava constantemente com expetoração, algo espessa e de cor transparente. De seguida, perguntei ao senhor se já se encontrava a fazer alguma medicação, ao qual ele respondeu que não sabia bem o que tomar ou fazer, e que teria apenas recorrido a rebuçado de mel.

Adicionalmente, perguntei se o senhor se encontrava a fazer algum tipo de medicação de forma crónica à qual ele respondeu que apenas tomava medicamentos para o colesterol, e desta forma pude perceber que os seus sintomas não estavam associados a nenhuma medicação. Continuei o atendimento, aconselhando-o a tomar o Fluimucil® (acetilcisteína) 600 mg comprimidos efervescentes, dissolvendo o comprimido num copo de água e tomando apena um por dia. Para além do expetorante, aconselhei-o a adquirir uma caixa de Strepfen® (flurbiprofeno) mel e limão, o qual deve dissolver na boca uma pastilha de cada vez, tomando no máximo um total de 5 pastilhas por dia, para aliviar os sintomas de garganta irritada.

Por fim como medidas não farmacológicas, aconselhei-o a beber muita água, dissolver outros rebuçados na boca de preferência sem açúcar, ingerir bebidas quentes, como por exemplo chá de mel e limão, elevar a cabeceira da cama para aliviar a tosse noturna e evitar inalação de pós e fumos, bem como mudanças bruscas de temperatura. Alertei-o ainda que se após 7 dias a sintomatologia não regredir, deve consultar um médico.

Caso Prático 5 - Conjuntivite alérgica

Uma senhora de cerca de 40 anos, deslocou-se à farmácia queixando-se de "visão baça, irritação no olho e excesso de remelas". Efetivamente, era visível as secreções esverdeadas no seu olho, bem como vermelhidão tanto no olho como em redor do mesmo. Comecei por questionar a senhora se costumava usar lentes de contacto, pergunta à qual a senhora respondeu negativamente, afirmando que nunca experienciou problemas de visão, mas que já há dois dias que sentia comichão no olho e que de manhã ao acordar tinha dificuldade em abrir o mesmo por excesso de secreções na zona interior da pálpebra. Prossegui, questionando a senhora se sentia dor ocular e desconforto em olhar para a luz, as quais ela respondeu que sim, mas que não se tratava bem de dor, mas sim mais uma sensação de desconforto.

Rapidamente percebi que se tratava de um caso de conjuntivite alérgica, e por isso perguntei a senhora se já teria iniciado algum tipo de tratamento, sendo que esta respondeu que apenas teria limpado o olho com algodão e água fresca. Expliquei-lhe que a conjuntivite alérgica se trata de uma inflamação que ocorre no olho e parte interior da pálpebra, e que esta normalmente origina prurido, vermelhidão e produção de secreções purulentas, sintomas estes que a senhora estava a experienciar, e que era normalmente provocada por excesso de pólen no ar ou outro tipo de alergénios.

Iniciei o aconselhamento e indiquei o uso de Allergodil® (azelastina) colírio, 0,5 mg/ml, sendo que deveria aplicar 1 gota em cada olho, duas vezes por dia. Adicionalmente, sugeri reforço da hidratação do olho com Systane Ultra® gotas oftálmicas, aplicando uma gota em cada olho entre 3 a 5 vezes ao dia, e ainda que efetuasse a limpeza do olho com os toalhetes Blephaclean® de manhã e à noite, antes da aplicação das gotas.

Por fim, como medidas não farmacológicas, aconselhei a senhora a evitar coçar os olhos, aplicar compressas frias nos olhos 3 a 4 vezes ao dia para reduzir a vermelhidão e prurido e evitar aplicar cosméticos tais como maquilhagem nos olhos até ter os sintomas controlados. Além disso, alertei para que se a sintomatologia não melhorasse num prazo de 7 dias, que deveria consultar um médico oftalmologista.

4 Considerações Finais

Ao longos dos meus cinco anos de MICF, tive a oportunidade de adquirir uma vasta quantidade de conteúdos teóricos que considerei essenciais para o sucesso da minha carreira como farmacêutica, no entanto estes tornar-se-iam inúteis se não os colocasse em prática, sendo que o Estágio Curricular se tornou a oportunidade perfeita o fazer.

Sinto que o meu estágio na Farmácia Miranda, juntou o "melhor dos dois mundos", teórico e prático, solidificando-os como um só. Após esta experiência sinto-me preparada para integrar uma equipa e para poder desempenhar o meu propósito como farmacêutica, ajudar, aconselhar e acima de tudo zelar pelo bem da população em geral.

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PARTE II

RELATÓRIO DE ESTÁGIO NO INFARMED - AUTORIDADE NACIONAL DO MEDICAMENTO E PRODUTOS DE SAÚDE, I.P.

Direção de Avaliação do Medicamento

Lista de Abreviaturas

AIM - Autorização de introdução no mercado

ARM - Assuntos regulamentares do medicamento

CAM - Comissão de avaliação das tecnologias de saúde

DAM - Direção de avaliação do medicamento

FFUC - Faculdade de farmácia da universidade de Coimbra

FI - Folheto informativo

INFARMED, I.P. - Autoridade nacional do medicamento e produtos de saúde, I.P.

MICF - Mestrado integrado em ciências farmacêuticas

RCM - Resumo das características do medicamento

ROT - Rotulagem

SWOT - Strengths, Weaknesses, Opportunities, Threats

I Introdução

O percurso académico de um estudante de Mestrado Integrado em Ciências Farmacêuticas (MICF) culmina na escolha, não só da área, como também do estabelecimento onde realizará o seu estágio curricular. Contrariamente às restantes Faculdades de Farmácia em Portugal, a Faculdade de Farmácia da Universidade de Coimbra (FFUC) destaca-se por oferecer aos alunos, e para além do estágio de carácter obrigatório em Farmácia Comunitária, um estágio adicional de três meses. Assim, existe um contacto próximo entre os alunos e as mais diversas áreas do mundo da Farmácia, que resulta na formação de profissionais completos a ingressar no mercado de trabalho.

Na minha ótica, esta é uma excelente oportunidade para, dentro do mundo do trabalho, experimentar, experienciar e aprender, facilitando, assim, a resposta à tão esperada questão: Qual é, então, o meu propósito neste que é um setor tão preponderante na nossa sociedade?

Ao longo da minha formação académica, várias foram as cadeiras que me despertaram entusiasmo, destacando-se, no entanto, as áreas da Comunicação e Marketing Farmacêutico, e de Assuntos Regulamentares.

Optei, então, e de acordo com os interesses supramencionados, por realizar o meu estágio na Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (INFARMED, I.P.), mais precisamente na Direção de Avaliação do Medicamento (DAM).

A área dos Assuntos Regulamentares é uma das múltiplas áreas que constituem a atividade farmacêutica, e exige um variado leque de conhecimentos em diversos ramos do domínio do medicamento e produto farmacêutico. Dentro deste domínio, os farmacêuticos não exercem a sua função, única e exclusivamente, na área do desenvolvimento do medicamento, exercendo, também, nas áreas do registo, introdução no mercado, posterior vigilância da sua utilização, bem como prestação de informação e apoio aos profissionais de saúde.

A minha determinação em integrar, temporariamente, a equipa do INFARMED, I.P., baseou-se, não só, no peso e significado dos assuntos regulamentares, como também, na oportunidade inigualável de integrar uma agência regulamentar, adquirindo, constantemente, novos conhecimentos, e obtendo, consequentemente, uma nova visão daquele que é o circuito do medicamento no contexto regulamentar.

Serve, assim, o presente relatório, para concretizar uma análise SWOT (*Strengths, Weaknesses, Opportunities, Threats*) no que diz respeito à minha experiência no estágio curricular, no contexto do Assuntos Regulamentares do Medicamento. Pretendo identificar, a nível interno, pontos fortes e pontos fracos, e a nível externo, as oportunidades e ameaças do meu estágio, que foi conduzido no INFARMED, I.P., sob a orientação da Dra. Dina Lopes, e

teve o seu início no segundo dia do mês de maio de 2023, e terminou no dia vinte e oito do mês de julho de 2023.

2 Enquadramento – INFARMED, I.P.

A Autoridade Nacional do Medicamento e Produtos de Saúde, I.P. (INFARMED, I.P.) surgiu em 1993, após a entrada de Portugal na Comunidade Económica Europeia (CEE), aquando da publicação do primeiro estatuto do medicamento resultante da transposição das diretivas europeias.[1] O INFARMED, I.P. é uma entidade estatal com um estatuto particular, definido por lei, atuando de uma forma indireta dentro da estrutura de administração pública do país. Possui independência administrativa, financeira e patrimonial, e é uma entidade autónoma nestes aspetos.[2]

O INFARMED, I.P. tem como principal objetivo regular e supervisionar todos os setores dos medicamentos de uso humano, bem como dos produtos de saúde. Desta forma, assegura a proteção da saúde pública, garantindo o acesso com qualidade, segurança e eficácia aos medicamentos, por parte dos profissionais de saúde e cidadãos[3].

Em termos de estrutura organizacional, o INFARMED, I.P. é constituído por cinco órgãos e treze unidades orgânicas, que se subdividem de acordo com a sua função, que poderá ser a de negócio ou a de suporte. Este instituto público encontra-se sedeado em Lisboa, mais especificamente no Parque da Saúde, sendo tutelado pelo Ministério da Saúde.

2.1 Direção de avaliação do medicamento (DAM)

Aquando do momento de decisão de estágio no INFARMED, I.P., optei pela DAM, cujo direção cabe à Dra. Marta Marcelino. Fui, então, integrada na equipa da Comissão de Avaliação do Medicamento, mais precisamente na Unidade de Introdução do Mercado (UIM), a qual é responsável pelo registo e autorização de medicamentos para entrada no mercado.

Dentro da UIM, trabalhei única exclusivamente com processos de reconhecimento mútuo e descentralizados, nos quais Portugal era estado membro envolvido. Durante o estágio, desempenhei funções de validação de submissões, isto é, executava a análise minuciosa da documentação e de informações essenciais, submetidas pela empresa. Após a dita análise, que era particularmente criteriosa, seguia-se o carregamento da base de dado GiMed, com posterior emissão do certificado de autorização de introdução no mercado (AIM), e que era enviado para aprovação e assinatura do mesmo. A par deste procedimento, fazia ainda a verificação dos textos submetidos, incluindo o Resumo das Características do Medicamento (RCM), o folheto informativo (FI) e a rotulagem (ROT).

3 Análise SWOT

Em conformidade com as normas orientadoras do estágio curricular, o presente relatório apresenta-se sobre a forma de análise SWOT, onde serão abordados, e no que ao meu estágio no INFARMED, I.P., diz respeito, os pontos fortes e os pontos fracos, numa vertente interna, e as oportunidade e ameaças, numa vertente externa.

3.1 Pontos Fortes

3.1.1 Acolhimento e Formação

Antes de iniciar o estágio, desloquei-me às instalações do INFARMED, I.P., a fim de poder receber todo o material necessário para iniciar a minha jornada enquanto estagiária.

Nesse mesmo dia, dirigi-me ao Departamento Informático, local esse onde se encontrava uma equipa a aguardar a minha chegada. Foi-me, assim, atribuído o número mecanográfico, e, após a criação do meu email institucional, sempre com a ajuda da aludida equipa, foi-me entregue um computador com acesso à rede interna do INFARMED, I.P., bem como a todas as plataformas que iria utilizar, nomeadamente GSUB, GiMed e SMUH-ALTER.

No meu primeiro dia de estágio fui recebida, de forma calorosa, pela Dra. Dina Lopes, que se apresentou como nossa Orientadora de Estágio. Numa breve reunião, foram-me explicadas as condições de estágio, aquilo que esperavam de mim enquanto estagiária, bem como todos os meus direitos e deveres. Finda a reunião, a Dra. Dina guiou-me numa visita às instalações, e apresentou-me à equipa com que trabalhei durante três meses, instalando-nos, de seguida, no escritório em que passámos esse período.

Os três primeiros dias foram dedicados à formação, onde me foi disponibilizado material didático, designadamente, vídeos e apresentações, cujo objetivo era aprofundar os conhecimentos que viriam a ser, por mim, aplicados. Para além disso, houve, ainda, uma formação intensiva, que durou cerca de cinco horas, e na qual aprendi a utilizar as ferramentas imprescindíveis para trabalhar com o GIMED.

Todos estes momentos de integração e formação foram bem estruturados e cruciais para um bom desenrolar do estágio.

3.1.2 Formação académica em Assuntos Regulamentares do Medicamento

A cadeira de Assuntos Regulamentares do Medicamento (ARM), ministrada sob a orientação do professor Doutor João José Sousa, foi a única abordagem incluída no plano de

estudos de MICF que retrata todo o processo de obtenção de uma AIM, bem como todas as complexidades inerentes a este processo.

Todo o conteúdo programático abordado por esta cadeira, bem como a sua estruturação, revelou ser de extrema importância ao longo de todo o estágio, estabelecendo um vínculo direto com todas as tarefas que desempenhei dentro do INFARMED, I.P.. A qualidade e organização desta cadeira resultou na perfeita assimilação e posterior adaptação, no que diz respeito às minhas responsabilidades dentro desta agência reguladora, o que contribuiu, substancialmente, para o meu bom desempenho.

Foi, efetivamente, exímia, a profundidade com que foram lecionados estes conteúdos, não havendo dúvidas de que, por essa razão, os estudantes de MICF da FFUC encontram-se numa posição privilegiada relativamente aos colegas de outras instituições a nível nacional, onde tal formação não possui caráter obrigatório.

3.1.3 Contacto direto e permanente com os requerentes AIM

Todas as tarefas que desempenhei durante o meu estágio tiveram por base uma comunicação constante com as diversas partes envolvidas no processo de desenvolvimento, registo e aprovação de um medicamento. Nesse contexto, deparava-me com situações que exigiam o pedido de elementos vários e a constante troca de emails, quer com o requerente da AIM, quer com outras autoridades reguladoras envolvidas no processo.

A diversidade de interações permitiu-me aprimorar a minha capacidade de comunicação, tanto em inglês como em português, bem como a minha abordagem profissional, ensinando-me a ajustar a minha comunicação consoante as situações com que me deparo.

Paralelamente, percebi que, e de forma a promover uma harmonização das metodologias de avaliação, é de extrema importância a comunicação entre diversas entidades reguladoras.

3.1.4 Responsabilidade e independência

Foi logo desde o início do estágio que me apercebi do elevado grau de responsabilidade que está associado às tarefas, por mim, desempenhadas. Ao longo do meu caminho enquanto estagiária, e consequente familiarização com toda a dinâmica circundante, percebi que, para além de responsabilidade, existia uma necessidade acrescida de deter autonomia e independência, não obstante o contacto direto e diário com os colaboradores, para qualquer esclarecimento de dúvidas.

Fui, inteiramente, responsável pela finalização dos processos que me foram designados, sendo que, muitas vezes, quando confrontada com cenários que me faziam duvidar das

capacidades de intervenção, conseguia desenvolver habilidades que resultaram em situações de sucesso, fruto da autonomia e confiança que foram, em mim, depositadas.

É, de facto, recompensante que, enquanto estagiários, nos sintamos valorizados, e, efetivamente, o INFARMED, I.P. concede-nos uma oportunidade de participar ativamente, sem que, em momento algum, seja colocada em causa a nossa importante função e credibilidade.

3.1.5 Duração do estágio

A duração do estágio, acordada entre a FFUC e o INFARMED, I.P. é de três meses, período esse que considero adequado, tendo em conta o facto de conseguirmos desenvolver, e de forma completa, o domínio pelo *software*, bem como a linguagem técnica.

Já a autonomia, e contrariamente ao suprarreferido, não chega a ser tão desenvolvida nestes três meses, dado o grande número de tarefas realizadas, bem como a abundância de conceitos a estas subjacentes.

Assim, considero que o período de estágio proposto é o correto e apropriado para adquirir as principais capacidades, indispensáveis à execução de tarefas comuns e quotidianas de uma agência reguladora.

3.2 Pontos Fracos

3.2.1 Foco único na finalização dos processos

Um dos pontos menos positivo, a meu ver, e no que ao meu estágio diz respeito, foi a monotonia associada às tarefas que desempenhei. A escassez de recursos humanos no INFARMED, I.P. é um problema real e atual que, de certa forma, condicionou o meu estágio curricular, uma vez que me foi atribuída total responsabilidade pela fase de finalização dos processos de atribuição de AIM. Nesta medida, os estagiários eram, efetivamente, os únicos colaboradores a efetuar este processo de finalização que, com o tempo, acabou por se tornar um procedimento mecânico e automático. Esta situação acabou, então, por impossibilitar a minha passagem por outras fases importantes, inerentes ao processo, como por exemplo a sua validação.

Pelo exposto, considero que uma maior dinamização das tarefas desempenhadas poderia ter tornado o estágio mais completo.

3.2.2 Sobrecarga dos colaboradores

A crise económica que assolou Portugal ainda antes da pandemia, bem como a crise que se gerou após a mesma, foi causa de uma afetação notória em diversos setores, e, de facto, o

sector das agências reguladoras não foi exceção. O corte orçamental levou a uma redução contínua do número de colaboradores; já o volume de trabalho, não só não reduziu, como se intensificou. A verdade é que este acontecimento originou uma menor capacidade de atuação, levando a que o INFARMED, I.P. esteja, atualmente, a trabalhar a um ritmo que não é o ideal, verificando-se uma acumulação crescente de trabalho. Esta situação, não só tem um forte impacto negativo no desempenho geral desta agência reguladora, como pode, igualmente, prejudicar a sua posição num panorama europeu.

O meu estágio decorreu durante este período crítico em que a equipa se encontrava limitada e sobrecarregada, o que, muitas vezes, levou a uma acumulação dos meus processos, bem como das minhas dúvidas, impedindo-me de prosseguir com as minha tarefas. Apesar de a equipa da DAM ter estado, sempre, disposta a esclarecer as dúvidas de todos os estagiários, a sobrecarga de trabalho foi impeditiva em alguns momentos em que, para nós, era fulcral a atenção da equipa, situação esta que causou algum impacto na nossa experiência.

3.3 Oportunidades

3.3.1 Participação em plenários da CAM

A Comissão de Avaliação dos medicamentos engloba um conjunto de peritos de diversas áreas, nomeadamente, médicos, toxicologistas, farmacêuticos, entre outros, que se reúnem de quinze em quinze dias, com o intuito de emitir pareceres relacionados com o medicamento, inclusive no domínio de avaliação da qualidade, eficácia e segurança dos medicamentos que, ou já se encontram no mercado português, ou visam essa entrada.[3]

No decorrer do meu estágio tive a oportunidade, que, a meu ver, foi extremamente enriquecedora, de assistir a uma das referidas reuniões plenárias, em que são tratados assuntos de cariz técnico-científico, e que, por sua vez, originam pareceres emitidos aquando da aprovação ou rejeição de uma AIM, o que me levou a um melhor entendimento acerca dos impactos dos aludidos pareceres neste tipo de decisões.

Importa, no entanto, salientar, que os assuntos discutidos no decorrer desta reunião são de cariz confidencial e sigiloso, não sendo, então, ético, da minha parte, abordá-los no presente relatório.

Infelizmente, a oportunidade surgiu numa fase tardia do estágio, e, apesar de todo o conteúdo ter uma forte correspondência com os conhecimentos por mim adquiridos durante o meu percurso académico, não teve muito impacto no desempenho das minhas tarefas, tendo em conta que decorreu no meu penúltimo dia de estágio. Porém, considero ter sido uma

excelente oportunidade para entender a importância da deliberação destes assuntos entre vários profissionais, e o impacto que estas decisões têm num ponto de vista regulamentar.

3.3.2 Perspetivas futuras após o estágio

A realização do estágio curricular na agência regulamentar nacional, INFARMED, I.P., concede aos estudantes uma visão holística de todo o método de atuação de uma agência regulamentar. Este contacto poderá vir a ser uma mais-valia numa possível e futura carreira na indústria farmacêutica, permitindo, assim, a escolha das melhores abordagens perante a autoridade regulamentar, antevendo possíveis constrangimentos aquando da submissão de um pedido de AIM.

A experiência e destreza por mim adquirida moldou-me enquanto futura farmacêutica, versátil e completa, concedendo-me a oportunidade de estar em vantagem relativamente aos meus colegas, aquando da entrada no mercado de trabalho.

3.4 Ameaças

3.4.1 Escassez de Recursos Humanos

Com o decorrer do meu estágio, foi percetível a escassez de recursos humanos, em paralelo com a considerável carga de trabalho atribuída aos colaboradores. Esta situação, que é, também, influenciada pela conjuntura económica do país, manifesta-se, não só, através da pouca disponibilidade no acompanhamento dos estagiários, como também nas tarefas que se encontram pendentes, não obstante os prazos existentes para que as mesmas sejam devidamente efetuadas.

Esta carência de supervisão influenciou, por diversas vezes, a celeridade e eficiência do meu trabalho. No entanto, foi, sempre, notório, um esforço por parte dos colaboradores para ajudar os estagiários, mormente através de marcação de reuniões de esclarecimento de dúvidas.

Em suma, considero que seria de extrema importância um reforço no departamento de recursos humanos da equipa UIM.

4 Considerações Finais

De forma a concluir o presente relatório, cumpre, salientar, que toda a minha experiência no INFARMED, I.P. foi consideravelmente positiva, revelando-se muito enriquecedora e proveitosa, já que me permitiu reconhecer a importância do farmacêutico no ramo dos Assuntos Regulamentares. Esta experiência só foi, por mim, vivenciada, devido à excecional

oportunidade concedida pela FFUC, que possibilitou, e continua a possibilitar, a todos os seus alunos, um estágio adicional, numa área que não a de Farmácia Comunitária e Farmácia Hospitalar.

Concretizando o sucesso do meu estágio em dois fatores, optaria pela incrível integração na equipa da UIM, que me permitiu uma aprendizagem coesa e contínua, não obstante as adversidades anteriormente mencionadas, e a formação ministrada ao longo do MICF, que foi completamente de encontro com aquilo que é a realidade profissional nesta área.

Sinto que finalizo esta experiência com ferramentas que me tornarão uma profissional completa, ágil e responsável, com todas as competências para, futuramente, poder vir a ingressar nesta área tão bonita que é o ciclo do medicamento.

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PARTE III

MONOGRAFIA

"Characterization of the pharmacotherapeutic evaluation processes of medicines used in the treatment of Inflammatory Bowel Diseases"

List of Abbreviations

Anti-TNFα - Tumor necrosis factor-alpha inhibitor

CATS - Portuguese health technology assessment commission

CD - Crohn's disease

CDAI - Chron's disease activity index

CMA - Cost-minimization analysis

CUA - Cost-utility analysis

EPAR - European public assessment report

GETAID - *Groupe d'étude thérapeutique des affections inflammatoires du tube digestif*

GRADE - Grading of recommendations assessment, development and evaluation

HAS - *Haute autorité de santé*

HTA - Health technology assessment

IBDQ - Inflammatory bowel disease questionnaire

IQWiG - Institute for quality and efficiency in health care

MAH - Marketing authorization holder

NHS - National health service

NICE - National institute for health and care excellence

NMA - Network meta-analysis

PAS - Patient access schemes

PDAI - Perianal disease activity index

PICO - Population, intervention, comparator and outcome

QALY - Quality-adjusted life years

SMC - Scottish medicines consortium

SmPC - Summary of the product characteristic

UC - Ulcerative colitis

Table Index

Resumo

A Doença Inflamatória Intestinal, que inclui a colite ulcerosa e a doença de Crohn, representa um desafio significativo para os cuidados de saúde. Definida por uma inflamação crónica, imuno-mediada em todo o sistema digestivo, a Doença Inflamatória Intestinal tem um impacto significativo na qualidade de vida do doente e nos sistemas de saúde.

Esta investigação conduz uma exaustiva análise comparativa dos relatórios de avaliação da eficácia relativa de três medicamentos principais - tofacitinib, ustekinumab e darvadstrocel - no âmbito do tratamento da doença de Crohn e da colite ulcerosa. O estudo centra-se nos relatórios de avaliação elaborados pela Comissão de Avaliação de Tecnologias de Saúde e, para proporcionar uma perspetiva mais alargada, inclui também uma extensa análise dos relatórios para os mesmos medicamentos elaborados por agências de Avaliação de Tecnologias de Saúde de renome: Haute Autorité de Santé, de França, National Institute for Health and Care Excellence, do Reino Unido, Scottish Medicines Consortium, da Escócia, e Institute for Quality and Efficiency in Health Care, da Alemanha.

A análise explora diferentes aspetos, incluíndo a população, a intervenção, os comparadores e os resultados selecionados pelas agências e pela empresa, a avaliação dos estudos selecionados, a avaliação metodológica, bem como a descrição da conclusão farmacoterapêutica.

Esta investigação procura reconhecer tanto pontos comuns como divergências entre as agências de ATS nos seus relatórios de avaliação, informando os processos de reembolso e melhorando as decisões que são tomadas com base em evidências ciêntificas.

Palavras-chave: Avaliação de Tecnologias de Saúde; Doença de Crohn; Colite ulcerosa; Relatórios de avaliação; Sistema de saúde; Financiamento.

Abstract

Inflammatory Bowel Disease, comprising ulcerative colitis and Crohn's disease, poses a significant healthcare challenge. Defined by chronic, immune-mediated inflammation within all digestive system, Inflammatory Bowel Disease has a significant impact on the patient's quality of life and healthcare systems.

This research leads an extensive comparative analysis of relative effectiveness assessment reports for three main drugs – tofacitinib, ustekinumab, and darvadstrocel – within the treatment of Crohn's disease and ulcerative colitis. The study focuses on the assessment reports made by the Portuguese Health Technology Assessment Commission, and to deliver a wider perspective, also comprises the comprehensive analysis of the reports for the same medications made by renowned Health Technology Assessment agencies: *Haute Autorité de Santé* from France, National Institute for Health and Care Excellence from the United Kingdom, Scottish Medicines Consortium from Scotland, and Institute for Quality and Efficiency in Health Care based in Germany.

The examination explores different aspects, including population, intervention, comparator, and outcomes selected by the agencies and the company, evaluation of the studies selected, the methodological assessment as well as description of the pharmacotherapeutic conclusion.

This research seeks to recognize commonalities and divergencies across health technology assessment agencies on their assessment reports, informing reimbursement processes and improving evidence-based decisions.

Keywords: Health technology assessment; Crohn's disease; Ulcerative colitis; Assessment report; Healthcare system; Reimbursement.

1 Introduction

1.1 Inflammatory Bowel Disease

Inflammatory Bowel Disease (IBD) is a term used to two distinct disorders, Crohn's disease (CD) and ulcerative colitis (UC), two "highly heterogeneous, debilitating, incurable, persistent, relapsing/worsening, immune-arbitrated inflammatory pathologies of the digestive system canal".[1] These two diseases differ in terms of pathophysiology, affected parts of the gastrointestinal tract, complications, symptoms, disease course and management.[2] It can occur in both males and females and most commonly appears in the early stages of life.[3] Moreover, if it remains for too long unchecked, can lead to a complicated disease course resulting in undesirable ramifications, like abscesses, fistulae, strictures, and bowel obstruction, as well as increased risk of gastrointestinal malignancy.[4]

Ulcerative colitis is a lifelong disease characterized by mucosal inflammation that normally starts in the rectum and continues to the colon.[5] The condition leads, in the earlier stages, to an inflammation and ulceration of the epithelial layer and later the submucosal layer, which can lead to bloody diarrhea, known as the predominant symptom.[1; 5]

Crohn's disease varies from UC in terms of location, usually takes place in all digestive system, from the mouth to the anus, and it can affect deeper layers than UC (mucosa, submucosa, muscularis, and serosa). Additionally, it is characterized by inflammatory areas interposed between normal mucosa, and it can also affect other organs besides the colon tract, through fistulation.[1; 2]

The cause of CD and UC is still unclear, but multiple factors can raise the odds of contracting this disease, like changed immune response, altered gut microbiota, genetic susceptibility, and environmental factors.[5]

Now, there is no standardized diagnostic test toll for IBD, and the identification of the disease relies on clinical, radiologic, endoscopic, and histopathologic analysis.[1]

The target outcomes for IBD are mucosal healing, reduced risk of surgery, lower relapse rates, and improved quality of life.[2] In other to achieve these outcomes, in the past two decades efforts have been made towards the biological treatment evolution, which is now considered the therapy of choice, particularly in patients with a high probability of disease progression.[2] Currently the options, besides de corticosteroid therapy are anti-tumor necrosis factor therapies like infliximab, adalimumab, and certolizumab, antagonist of IL-12 and IL-13 signaling (ustekinumab), gut-selective monoclonal anti-integrin antibody (vedolizumab), and small molecule therapy (tofacitinib).[4] Some choices, besides being promising, they come with a risk of immunogenicity, and its parenteral administration isn't the most comfortable option.[2]

1.2 Health Technology Assessment (HTA)

Health Technology Assessment is described as "a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of health technology in a systemic, transparent, unbiased, robust manner"[6] to create safe and effective evidence, about not only medicines but medical devices as well, that perform as a vital tool for decision-makers and stakeholders, supporting policy-level decision-making in healthcare. It acts as a bridge between the fields of research and policy-making, enabling informed choices to improve healthcare practices.[7; 8]

In the decision-making, various factors are considered, not limited to the standard criteria of quality, safety, and efficacy required for all drugs. The process also involves assessing comparative effectiveness criteria to ensure the most efficient use of the available resources.[8]

Currently, almost all European Union Member States have introduced HTAs, as a reliable source of evidence to support decisions that impact the healthcare system.[9] The approach and methods utilized by the different HTA agencies differ considerably across the different countries[9] and this research aims to someway evaluate the assessment reports and highlight the differences between them.

1.3 HTA in Portugal

The HTA has played a major role in Portugal since 1999, as it has been used to assess medications as part of reimbursement processes and, later in 2007, for pre-evaluation before funding decisions. In 2015, when the National Health Technology Assessment System (SiNATS) was created, it was fixed that the scope of HTA should include other health technologies like medical devices and evaluating technologies throughout their life cycle.[10]

HTA includes collaboration between experts from different fields, pharmaceutical, clinical, and economic, working within the Health Technology Assessment Directorate (DATS) and the Health Technology Assessment Commission (CATS). CATS, established to support DATS that carries the authority to provide opinions on health technology evaluation, funding, and public health interests within SiNATS.[10]

The public funding process in Portugal settles into five important phases: application submission, pharmacotherapeutic evaluation, pharmacoeconomic evaluation, negotiation, and final decision-making.[10] This research will focus mainly on the pharmacotherapeutic evaluation.

Within the pharmacotherapeutic evaluation, the first important step is to define the evaluation matrix, more commonly known as PICO. PICO is an acronym for population, intervention, comparators, and outcomes, and is used in evidence-based medicine, to

structure and address a clinical or medical care question. This framework is also essential for developing effective literature search strategies, such as in systematic reviews.[8]

Next, the focus shifts to defining the population under evaluation, considering the clinical characteristics of the population included in the therapeutic indication. After the population the intervention under evaluation should be precisely defined, ensuring that it comprises only the specific treatment being studied. Also, the comparators play a pivotal role in the evaluation process. These must be the therapeutic alternatives approved to be used in Portugal to treat the same indication of the medicine under evaluation, with the purpose of determining its additional benefits and cost-effectiveness.[8]

Finally, the last point selected for the PICO framework is the outcomes. These should be relevant to assess the effectiveness and safety of the intervention, and a well-rounded perspective of the treatment's impact should be ensured, incorporating outcomes that matter the most to the patients.[8]

The next step is to evaluate the added therapeutic value using a methodology of evidence-based medicine. This methodology analyzes the comparative and randomized clinical trials that should have been incorporated in a systematic review, and all evidence consider relevant by INFARMED, considering that all evidence should be provided by the company holding the Marketing Authorization.[8] It is important to refer that the quality of the evidence should be assessed since it reflects the confidence of the conclusions.

The last crucial step involves drawing a pharmacoeconomic conclusion. Firstly, relevant data on the economic aspects, such as intervention costs, are collected. Secondly, these costs are compared with those of the comparators under analysis. This allows a cost-effectiveness analysis to determine whether the new intervention provides value for money compared to the comparators. Additionally, a budget impact analysis is essential to estimate, the financial impact of adopting the new healthcare technology on the healthcare system. This analysis considers factors like number of patients who would receive the intervention, the cost of the intervention, and the potential saving and costs associated.[11]

Lastly, the negotiation process between INFARMED and the MAH takes place, and finally, a decision is made and published through a public report.[10]

This is a very illustrative scheme of the National System for the HTA (SiNATS).[12]

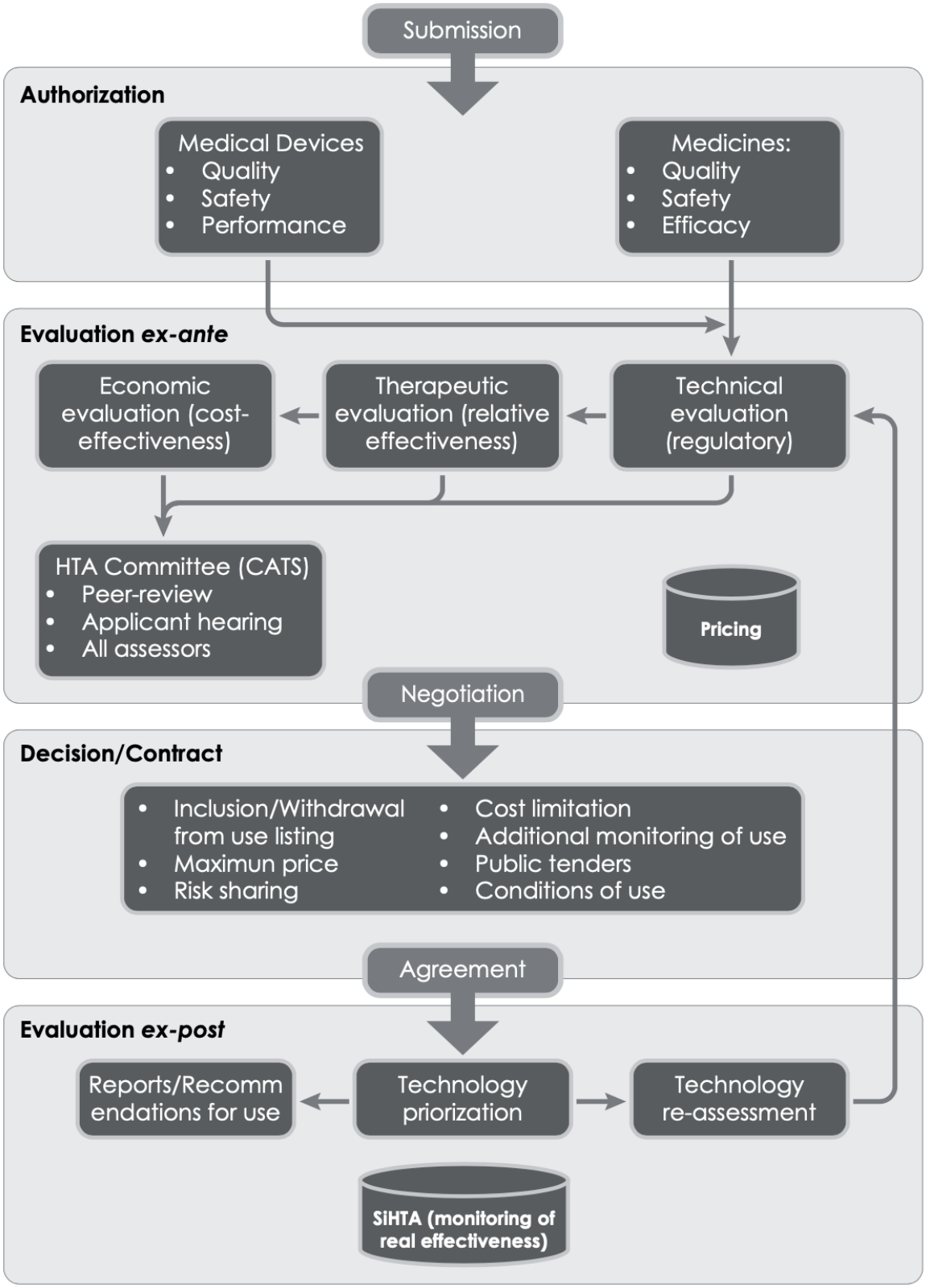

Figure 1- Scheme of the National System for the HTA (SiNATS)[12]

2 Objective

This research is aimed at comparing the relative effectiveness assessments of drugs indicated to treat Inflammatory Bowel Diseases that were produced by the Portuguese Health Technology Assessment (HTA) Agency with the assessments performed by other Health Technology Assessment (HTA) agencies, including *Haute Autorité de Santé* (HAS) from France, National Institute for Health and Care Excellence (NICE) from the United Kingdom, Scottish Medicines Consortium (SMC) from Scotland and finally the Institute for Quality and Efficiency in Health Care (IQWiG) based in Germany. By conducting this comparison, the purpose of this study is to identify both divergencies and similarities within these assessment procedures and to discuss those differences through the in-depth analysis of the important points like the population under study, choice of the comparators, selection, and significance of the outcomes, and number and type of the reviewed studies as well as the pharmacotherapeutic conclusion.

3 Methodology

The research design employed in this thesis is a comparative analysis to evaluate assessment reports of three medicines, Tofacitinib, Ustekinumab, and Darvadstrocel, focusing only on their indication for Crohn's disease (CD) and ulcerative colitis (UC). The research centers on the analyses of relative effectiveness assessment reports that were carried out by the Portuguese Health Technology Assessment Commission (CATS) from May 2020 until the end of 2022. This period of time was chosen as the starting point because it marks the introduction of a new format for CATS relative effectiveness assessment reports, which specify information such as Population, Intervention, Comparator, and Outcome (PICO), evaluation of the studies, and the methodological assessment, as well as description of the pharmacotherapeutic conclusion.

To provide a broader and comparative perspective, the relative's effectiveness assessment reports for the medicines aforementioned produced by other Health Technology Assessment (HTA) agencies, including *Haute Autorité de Santé* (HAS) from France, National Institute for Health and Care Excellence (NICE) from the United Kingdom, Scottish Medicines Consortium (SMC) from Scotland and finally the Institute for Quality and Efficiency in Health Care (IQWiG) based in Germany, were reviewed. The decision to include these agencies in this research stems from their strong standing, reputation, and significant impact within the European context.

The purpose of this thesis is to compare the main characteristics of the relative effectiveness assessment conducted in Portugal with the assessments conducted in the selected countries for the same drugs. This analysis took into consideration the following aspects: therapeutic indication considered on the Summary of the Product Characteristic (SmPC), therapeutic indication proposed for funding, PICO defined in phase III clinical trials of the clinical development program of the drugs, PICO defined by the HTA agency, type and the number of the trials considered for the HTA agency, the conclusion of the therapeutical evaluation, and overall quality of the evidence.

The goal was to find similarities and divergences in the relative effectiveness assessment procedure, with the aim of supporting and optimizing reimbursement processes and aiding evidence-based decision-making in healthcare systems.

4 Results and Discussion

4.1 Ulcerative colitis

4.1.1 Ustekinumab (Stelara)

Therapeutic indication proposed for funding and considered in the SmPC

As mentioned above, this analysis focuses on key aspects of the technological assessment, starting with ustekinumab for ulcerative colitis.

Table 1 - Therapeutic indication considered on the SmPC and proposed for funding for ustekinumab with indication for the treatment of UC.

Therapeutic indication considered on the SmPC for ustekinumab	
"STELARA is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies."[13]	
Therapeutic indication proposed for funding for ustekinumab	
CATS	"Treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies."[14]
NICE	" People with moderately to severely active ulcerative colitis who are intolerant of, or whose disease has had an inadequate response, or loss of response to previous biologic therapy (a TNF-alpha inhibitor or vedolizumab), or a JAK inhibitor (tofacitinib), or conventional therapy (oral corticosteroids and/or immunomodulators)."[15]
SMC	"For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies."[16]
HAS	"Treatment of moderate to severe active ulcerative colitis in adults, as 3rd line treatment, in the event of failure (insufficient response, loss of response, intolerance or contraindication) of conventional treatments (5- amino salicylates, corticosteroids and immunosuppressants) and at least one biological drug among anti-TNFα and vedolizumab."[17]

Firstly, the therapeutic indication considered in the SmPC and the proposed indications for funding provided by the selected HTA agencies were analyzed. Defining the intervention is one of the first steps made at the beginning of structuring the framework for estimating clinical and cost-effectiveness, it should include the patient's groups considered, comparators, and the expected place on the pathway care[18]. This is a common step in all methodologies considered by HTA agencies in this research.

As stated in the SmPC, ustekinumab is indicated for the treatment of adult patients diagnosed with two forms of active ulcerative colitis, ranging from moderate to severe. However, it should only be considered for patients who have had an inadequate response, either due to loss of response or intolerance, to both conventional or biological therapy or those who have medical contraindications to such therapies.

The CATS and SMC assessment reports aligned closely with what is described in the SmPC in terms of indication prevue for funding. On the other hand, HAS states that ustekinumab besides what is indicated by the SmPC, should also be used as a third line of treatment. Moreover, HAS emphasizes 5-amino salicylates, corticosteroids, and immunosuppressants as conventional therapy, and states that ustekinumab must only be used after failure of at least one biological drug among anti-TNFα and vedolizumab.

NICE decided to consider for evaluation ustekinumab within the indication for treating moderately to severely ulcerative colitis when an anti-TNF, vedolizumab, tofacitinib, or conventional therapy has failed, cannot be tolerated, or isn't suitable.

These diversities in terms of therapeutic indications throughout the relative effectiveness assessment reports underline the nuanced perspectives and approaches of each HTA agency and their specific criteria for ustekinumab´s use in UC management.

PICO considered in the phase III clinical trials and in the assessment reports

In the context of clinical trials, PICO stands for Patient/Population, Intervention, Comparator, and Outcome, and helps define the key components of a study and facilitate the recovery of important evidence.

In the European Public Assessment Report (EPAR) for a phase III clinical trial, the PICO elements are used to explain the trial design and give a clear understanding of the study´s objectives. HTA agencies use an identical PICO framework to assess the clinical effectiveness, safety, and cost-effectiveness of interventions. PICO is selected according to the available evidence, clinical guidelines, and specific objectives of the assessment. The chosen comparators and outcomes in the HTA reports should align with those used in the clinical trials.[19]

The second step involves establishing the target population for the assessment report. It is crucial to encompass all subjects for whom the technologies are being evaluated as precisely as possible. If applicable, should identify subpopulations for whom indication might differ from the overall population or could need more meticulous considerations.[8; 18]

The population considered, in the phase III clinical trials were adult subjects with moderately to severely active UC who have formerly undergone treatment with one or more anti-TNFα or vedolizumab, or subjects who are naïve to the biologic treatments and had an inadequate response, lost response, or failed to accept the conventional treatment for UC, which include corticosteroids and immunomodulators, as azathioprine and 6-mercaptopurine.[20]

When it comes to the HTA agencies, CATS, SMC, and HAS considered the exact same population as the clinical trials[14; 16; 17]. On the other hand NICE had a more conservative approach since it considered a very similar population with the difference that besides choosing people who have failed the biologic agents and conventional therapy, people who also failed JAK inhibitors, like tofacitinib were also enclosed[21].

It is essential to emphasize, that the initial population chosen for the health technology assessment may not always be the population chosen for reimbursement and acceptance by the NHS. This variation can occur due to company selling strategies, and sometimes because the evaluation led to a conclusion that the population must be restricted or modified.

The third point analyzed was the comparators and outcomes considered in the phase III trials conducted by the company and the ones selected by HTA agencies for inclusion in their assessment reports.

In a relative effectiveness assessment, a comparator refers to a healthcare intervention or other technology applied to make a comparison or determine whether the intervention or technology under evaluation provides an additional therapeutic benefit.[21] Therefore, under ideal conditions a perfect comparator would be the reference treatment with high-quality clinical practices at the European and international level, which has excellent quality evidence, in both efficacy and safety profiles, and with a European marketing authorization or another regulatory method of approval for the indication and line of treatment under assessment.[21]

However, in many circumstances, consensus is difficult to achieve across European countries on what is considered routine clinical care. The choice of comparators might be biased and occasionally is governed by the legislation, and in some cases refer to cost, and in other cases is governed by the intention to understand as much as possible about the new health technology.[21]

Regarding the outcomes selected for ustekinumab, the outcomes of the induction phase had to be separated from those of the maintenance phase, as well as discriminating the primary and secondary outcomes or critical and important outcomes.

It is important to note, that the following information displayed in the next table was entirely extracted from assessment reports of the different HTA agencies.

Table 2 - Comparators and outcomes considered in the phase III trials and considered by the HTA agencies for ustekinumab with indication for the treatment of UC.

<table>
<tr><th colspan="3">Comparators and outcomes considered in the phase III trials for ustekinumab</th></tr>
<tr><td colspan="3">Comparator: placebo[20]</td></tr>
<tr><td colspan="2">Induction phase outcomes
<u>Primary outcomes:</u>
• Clinical remission as week 8 [I]
<u>Secondary Outcomes:</u>
• Endoscopic healing at week 8 [II]
• Clinical response at week 8 [III]
• The change from induction baseline in the total score of the Inflammatory Bowel Disease Questionnaire (IBDQ) at week 8
• Mucosal healing at week 8.[IV20]</td><td>Maintenance phase outcomes
<u>Primary outcomes:</u>
• Clinical remission at week 44
<u>Secondary outcomes:</u>
• Maintenance of the clinical response through week 44
• Endoscopic healing at week 44
• Clinical remission and not receiving concomitant corticosteroids at week 44
• Maintenance of clinical remission through week 44 among the subjects who had achieved clinical remission at maintenance baseline. [20]</td></tr>
<tr><th colspan="3">Comparators and outcomes considered by the HTA agencies for ustekinumab</th></tr>
<tr><td>CATS</td><td colspan="2">Comparators: Infliximab, adalimumab, golimumab and vedolizumab[14]

Outcomes
<u>Critical outcomes:</u>
• Induction of remission of UC
• Maintenance of remission of UC
• Improvement in quality of life
• Hospitalization rate due to UC
<u>Important outcomes:</u>
• Induction of partial response of UC
• Endoscopic remission (mucosal healing)
• Histological improvement
• Reduction in corticosteroid therapy in patients receiving corticosteroids[14]
<u>Critical safety outcomes:</u>
• serious adverse events
• adverse events leading to discontinuation
• opportunistic infections
• mortality
<u>Important safety outcomes:</u>
• adverse event rate[14]</td></tr>
</table>

<table>
<tr><td rowspan="2">NICE</td><td colspan="2">Comparators: anti-TNFα (infliximab, adalimumab and golimumab), vedolizumab, tofacitinib, conventional therapies without biological treatments[15]</td></tr>
<tr><td colspan="2">Outcomes measures to be considered
Mortality
Measures of disease activity
Rates of and durations of response, relapse and remission
Rates of hospitalization
Rates of surgical intervention
Endoscopic healing
Mucosal healing (combined endoscopic and histological healing)
Corticosteroid-free remission
Adverse effects of treatment
Health-related quality of life[15]</td></tr>
<tr><td rowspan="2">SMC</td><td colspan="2">Comparators: Vedolizumab, adalimumab, infliximad, golimumab, tofacitinib[16]</td></tr>
<tr><td>Induction phase outcomes
Clinical remission
Endoscopic improvement
Clinical response
Baseline IBDQ Score
Change from baseline in total IBDQ Score
Histo-endoscopic mucosal healing[16]</td><td>Maintenance phase outcomes
Clinical remission
Maintaining clinical response
Endoscopic improvement
Clinical remission and not receiving corticosteroids
Clinical remission at baseline
Maintaining clinical remission[16]</td></tr>
<tr><td rowspan="2">HAS</td><td colspan="2">Comparators: infliximab, adalimumab, golimumab and its biosimilars, vedolizumab and tofacitinib[17]</td></tr>
<tr><td>Induction phase outcomes
<u>Primary outcomes:</u>
Clinical remission at week 8
<u>Secondary Outcomes:</u>
Percentage of patients with mucosal healing
Percentage of clinical response
Quality of life: change in IBDQ total score
Histo-endoscopic mucosal healing[17]</td><td>Maintenance phase outcomes
<u>Primary outcomes:</u>
Clinical remission at week 44
<u>Secondary outcomes:</u>
Maintenance of clinical response
Endoscopic healing of the mucosa
Clinical remission without the use of corticosteroids
Maintenance of clinical remission[17] [I]</td></tr>
</table>

I Clinical remission was defined as a Mayo score ≤2 points, with no individual subscore >1.
II Endoscopic healing was defined as an endoscopy subscore of the Mayo score of 0 or 1.
III Clinical response was defined as a decrease from baseline in the Mayo score by ≥ 30% and ≥ 3 points, with either a decrease from baseline in the rectal bleeding subscore ≥ 1 or a rectal bleeding subscore of 0 or 1.
IV Mucosal healing was defined as a combination of histologic healing and endoscopic healing. Histologic healing, based on features of the Geboes score, was defined as neutrophil infiltration on < 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue.

When comparing the selection of comparators and outcomes between the phase III clinical trials of the clinical development program of the drugs conducted by the company for ustekinumab with the comparators and outcomes assessed by the HTA agencies, there are some discrepancies and commonalities.

The company´s trials mainly utilized a placebo as the comparator. Conversely, the HTA agencies (CATS, NICE, SMC, and HAS) considered a wider range of comparators, including

other biologic agents, such as anti-TNFα (infliximab, adalimumab, and golimumab), vedolizumab, JAK inhibitor (tofacitinib), and lastly conventional therapies were also included.

The explanation behind the differences in the selection of the comparators made by the company and the HTA agencies could be related to variations in the focus of their assessments as well as the outcomes considered as primary and secondary.

The company, when designing ustekinumab clinical trials, they selected comparators that they deemed to showcase the ustekinumab's advantages and efficacy, directing towards the demonstration of its possible superiority over other treatments. In contrast, HTA agencies as independent evaluators, normally consider a broader range of comparators to secure a comprehensive and unbiased evaluation.

The divergent choice of comparators may also be explained through the main goal of each party. While the company's goal is to emphasize outcomes that highlight ustekinumab's attributes in order to gain regulatory approval and market acceptance, the HTA agencies account for public health interests, pursuing to determine the most cost-effective treatment options.

The comparators are intimately related to the choice of the outcomes. In terms of commonalities the company and HTA agencies, assessed clinical remission as an important primary outcome during both the induction phase as well as in the maintenance phase of the ustekinumab treatment. This appoints clinical remission as a measure of treatment success and disease control.

Other outcomes were considered, such as induction of clinical response, endoscopic healing, improvement in quality of life monitored by changes in the IBQD Score, mucosal healing, and clinical remission with reduction or suppression of the corticosteroid therapy. These outcomes were commonly observed in both clinical trials and relative effectiveness assessment reports, although they were mostly considered secondary outcomes. These outcomes provide a more clear and more comprehensive assessment of the ustekinumab's overall impact on the disease and patient's life.

However, CATS and NICE contrarily to the company, SMC, and HAS, considered rates of hospitalization and surgical intervention as an important outcome for treating UC with ustekinumab. Choosing these specific outcomes suggests that CATS and NICE take a wider view of the influence of the treatment on healthcare utilization and overall patient outcomes, as these reflect the real-world impact of the drug on managing the disease severity.

Additionally, unlike the other HTA agencies, CATS included safety outcomes in its assessment report, categorizing them as critical outcomes: serious adverse events, adverse events leading to discontinuation, opportunistic infections, and mortality. CATS considers as

critical, all crucial safety measures that can directly impact patient well-being and treatment compliance.[8] Furthermore, as important outcomes, serious adverse events are relevant to understand the ustekinumab safety profile besides not being a life-threatening measure.

In conclusion, the divergencies in the choice of comparators and outcomes between the HTA agencies regarding the assessment of the effectiveness of ustekinumab can be justified by the different regulatory requirements between countries.

Number and type of studies included on the assessment reports by the HTA agencies

In order to make comprehensive considerations and draw more robust conclusions, the HTA agencies relied on the phase III clinical trials from the clinical development program of the drugs, carried out by the company – "A Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of ustekinumab induction and maintenance therapy in subjects with moderately to severely active ulcerative colitis" – UNIFI-I and UNIFI-M.[20] Moreover, apart from the clinical trials, a systematic review of the literature was performed by the company to identify all randomized studies on the efficacy and safety of various therapeutic options, including ustekinumab, infliximab, adalimumab, golimumab, tofacitinib, and vedolizumab, in patients intolerant or after failure of biological therapies.[14] This network meta-analysis (NMA) granted a wider understanding of the indirect comparisons, between ustekinumab and its comparators.

Furthermore, SMC considered not only one NMA, but created a systematic review were inserted twelve different NMAs submitted by the company[16], while HAS considered 2[17], CATS only considered one NMA[14], and NICE relied on multiple NMAs from the induction and maintenance phase.[22]

The process of electing evidence to be considered in the assessment of a new drug can be different among HTA agencies. Some agencies, like SMC and NICE, opt for a comprehensive approach, considering a bigger volume of evidence to build a more robust case. Others, like CATS and HAS, focus only on critical and impactful evidence that offers clear support for their relative's effectiveness assessment, thus considering less evidence. These variations can be justified by the different agency strategies, and the necessity to balance efficiency with ensuring careful evaluations.

Conclusion of the therapeutical evaluation

The conclusions of the therapeutical evaluation drawn by CATS, NICE, SMC, and HAS, regarding the use of ustekinumab in the treatment of ulcerative colitis, varied in their relative effectiveness assessment reports.

From the CATS perspective, ustekinumab showed comparable efficacy to infliximab, adalimumab, golimumab, and vedolizumab in inducing remission (primary outcome) in patients who had an inadequate response or intolerance to conventional therapy. When it comes to patients with inadequate or intolerant responses to both conventional and biological therapy, ustekinumab showed evidence of superiority over adalimumab and comparability to vedolizumab.[14]

NICE acknowledged that ustekinumab and vedolizumab have distinct mechanisms of action compared to anti-TNFα, therefore they concluded that ustekinumab can be recommended as a treatment option for the indication under analysis, but only when conventional therapy or a biological agent cannot be tolerated or has shown inadequate response.[22] NICE, as well as SMC, noted that ustekinumab may be preferred over vedolizumab due to its mode of administration which is a subcutaneous injection after 8 or 12 weeks rather than intravenous injection of vedolizumab at 0, 2, 6 weeks and then 8 weeks thereafter, that can be transposed in less impact in patients and service, which showed awareness by the quality of life of the patients.[16; 22; 23] Furthermore NICE valued the fact that ustekinumab not only acts mainly in the gut, like vedolizumab but also acts on other manifestations of the disease, such as skin and joints.[22] In conclusion, NICE considered ustekinumab more effective than a placebo and comparable to the other treatments.[21]

In addition to the aforementioned points, SMC reinforced its analysis with the NMAs provided by the company. Based on this analysis, SMC suggested that ustekinumab is likely comparable to vedolizumab, adalimumab, golimumab, infliximab, and tofacitinib in both the induction and maintenance phases. As per the clinical experts consulted by SMC, they recommend that ustekinumab should be considered primarily for patients who have experienced treatment failure with anti-TNFα therapies.[16]

In contrast to the other HTA agencies, HAS determined that ustekinumab's actual benefit is considerable only as a third-line treatment option for UC in adult patients who have failed not only conventional treatments and at least one anti-TNFα but also vedolizumab. Taking this into consideration, HAS did not find ustekinumab to be superior to vedolizumab or the other comparators.[17]

In summary, the HTA agencies presented divergent conclusions. CATS emphasized its comparable efficacy as well as SMC, NICE recommended it as an option with benefits over vedolizumab and HAS recognized its efficacy but limited use to third-line treatments without superiority to vedolizumab or other comparators.

As suggested from the analysis of the above information, CATS and SMC of all agencies, have taken a less conservative and distinctive stance. These two agencies consider ustekinumab as a potential first option of treatment following the failure of conventional therapy. Furthermore, CATS has expressed the belief that ustekinumab is superior to adalimumab, a viewpoint not shared by the other agencies.

Conversely, the other HTA agencies adopted a more cautious approach, stating that ustekinumab should only be considered after the failure of both conventional and biological therapy. Consequently, they do not put ustekinumab at the same level as adalimumab, golimumab, tofacitinib, and infliximab. Instead, these agencies, only regard ustekinumab as comparable to vedolizumab.

The divergence in conclusions can be explained through several factors such as budget constraints or perceived differences in effectiveness and safety profiles and the varying interpretations and recommendations underline the complexities innate to health technology assessments and emphasizes the need for a comprehensive evaluation of all relevant evidence to inform the stakeholders.

Another relevant aspect is the overall quality of the evidence provided by the company, which is included in the new format for CATS relative effectiveness assessment reports. For ustekinumab in the treatment of UC, CATS states that the submitted evidence has moderate quality when it comes to the analysis made for the induction phase and low quality in the maintenance phase, which accordingly to CATS gives a high degree of uncertainty in the results for the maintenance phase.3 NICE as well as CATS, mentioned that the quality of the evidence was also of low quality. [22]

These two agencies are the only ones to provide this kind of information in their assessment reports. CATS issued in 2016 some guidelines about their main procedures regarding the evaluation of the added therapeutic value of emerging technology. These specific guidelines adopt a methodology similar to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE).[24]

GRADE is a transparent framework that was developed as a sensible and clear approach to rating the quality or certainty of evidence and the strength of recommendations made by the HTA agencies.[25]

According to the GRADE framework, the primary steps, include choosing the appropriate comparators and outcomes in accordance with the clinical question. The next step consists in rating the quality of the evidence, which often varies between the outcomes. GRADE considers four levels of evidence, reflecting their certainty.[26]

Normally, evidence from randomized controlled clinical trials initiates as high quality, and evidence from observational trials serves as a starting point for low-quality evidence.[26]

CATS assessing the outcomes of the induction phase rate them as being of moderate quality, which suggests that the true effect is probably near to the estimated effect. The outcomes from the maintenance phase being considered of low quality indicates that the true effect might be different from the estimated effect.[14; 26]

4.1.2 Tofacitinib (Xeljanz)

Therapeutic indication proposed for funding and considered in the SmPC

The study also encompassed the investigation of tofacitinib for the treatment of ulcerative colitis, entailing analysis of its indication and other pertinent aspects of its relative effectiveness assessment report. Starting with comparing its therapeutic indication considered on the SmPC with its therapeutic indication proposed for funding.

In this research were all included the relative effectiveness assessment report from IQWiG.

Table 3 - Therapeutic indication considered on the SmPC and proposed for funding for tofacitinib with indication for the treatment of UC.

Therapeutic indication considered on the SmPC for tofacitinib	
"Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent."[27]	
Therapeutic indication proposed for funding for tofacitinib	
CATS	"Tofacitinib is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent."[28]
NICE	"People with moderately to severely active ulcerative colitis who are intolerant of, or whose disease has had an inadequate response or loss of response to conventional therapy (oral corticosteroids and/or immunosuppressants) or a TNF-alpha inhibitor."[29]
SMC	"For the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response lost response or were intolerant to either conventional therapy or a biologic agent."[30]
HAS	In the treatment of moderate to severe active ulcerative colitis in patients who have failed (insufficient response, loss of response or intolerance) to conventional treatment (with 5-aminosalicylates, corticosteroids and immunosuppressants) and to anti-TNFα.[31]
IQWiG	"Treatment of adult patients with moderately severe to severely active ulcerative colitis who have responded inadequately to, no longer respond to, or do not respond to conventional therapy or a biological agent."[32]

As stated on the SmPC, tofacitinib has an indication on the treatment of moderate to severe UC, when the use of conventional and biologic therapy is not available, because of lost or inadequate response or intolerance to such therapies.

As presented in the table above we can observe that the therapeutic indication proposed for funding by the HTA agencies, aligned perfectly with the indication stated on the SmPC.

This alignment guarantees that tofacitinib is being evaluated for the precise population for whom its clinical benefits are most relevant, and it showcases the agencies' dedication to aligning their assessments with the established clinical parameters defined for the company. Furthermore, this coordination improves the effectiveness of the treatment assessment as well as the funding and acceptance process.

PICO considered in the phase III clinical trials and in the assessment reports

When it comes to the analyses of the PICO considered for both company and HTA agencies, the population was the first point analyzed. The population selected for the studies by the company were: patients diagnosed with moderate to severe ulcerative colitis for at least 4 months, and the subjects must have failed or showed intolerance to at least one corticosteroid approved for therapy and an anti-TNFα.18 The population chosen for the assessment reports lined up closely with the one chosen for the company, except for the specified time frame for the duration of the diagnosis. [28; 30; 31; 32; 34]

This line-up in the selection of the population ensures that the study population corresponds directly to the target patient group for whom the intervention is designed and strengthens the validity of the assessment process.

The second point analyzed was the comparators and outcomes.

Table 4 - Comparators and outcomes considered in the phase III trials and considered by the HTA agencies for tofacitinib with indication for the treatment of UC.

Comparators and outcomes considered in the phase III trials for tofacitinib	
Comparator: placebo[33]	
Induction phase outcomes	**Maintenance phase outcomes**
<u>Primary outcomes:</u> • Clinical remission as week 8 <u>Secondary Outcomes:</u> • Mucosal healing at the end of week 8 • Clinical response at the end of week 8 • Endoscopic remission at the end of week 8 • Clinical remission at the end of week 8 • Symptomatic remission at the end of week 8 • Complete remission at the end of week 8 <u>Other outcomes</u> • Change in the total IBDQ score[33]	<u>Primary outcomes:</u> • Remission at the end of week 52 <u>Secondary outcomes:</u> • Mucosal healing at the end of week 52 • Discontinuation of corticosteroid therapy in patients in remission at study initiation • Continuous remission at the end of week 24 and 52 • Mucosal healing at the end of week 24 and 52 • Continuous clinical response at the end of week 24 and 52[33]

Comparators and outcomes considered by the HTA agencies for tofacitinib		
CATS	**Comparators:** Infliximab, adalimumab, golimumab and vedolizumab[28]	
	Outcomes Critical outcomes: • Hospitalization rate • Surgical intervention rate • Clinical disease activity measures • Quality of life assessed by validated scales Important outcomes: • Endoscopic mucosal healing[28] Critical safety outcomes: • Mortality • Incidence of adverse effects • Discontinuation due to adverse effects • Increased rate of opportunistic infections and infestations • Increased rate of neoplasms Important safety outcomes: • overall incidence of adverse effects[28]	
NICE	**Comparators:** anti-TNFα (infliximab, adalimumab and golimumab), vedolizumab, conventional therapies without biological treatments[29]	
	Outcomes measures to be considered • Mortality • Measures of disease activity • Rates of and durations of response, relapse and remission • Rates of hospitalization • Rates of surgical intervention • Time to surgical intervention • Achieving mucosal healing • Adverse effects of treatment • Health-related quality of life[29]	
SMC	**Comparators:** Vedolizumab, adalimumab, infliximad, golimumab[30]	
	Induction phase outcomes Primary outcomes: • Remission at week 8 Secondary outcomes: • Mucosal healing a week 8 • Clinical response at week 8 • Endoscopic remission at week 8[30]	**Maintenance phase outcomes** Primary outcomes: • Remission at week 52 Secondary outcomes: • Mucosal healing at week 52 • Sustained corticosteroid-free remission at week 52 • Clinical response at week 52[30]
HAS	**Comparators:** infliximab, adalimumab, golimumab and its biosimilars, vedolizumab[31]	
	Induction phase outcomes Primary outcomes: • Remission at week 8 Secondary Outcomes: • Mucosal healing ate week 8 • Clinical response at week 8 • Quality of life[31]	**Maintenance phase outcomes** Primary outcomes: • Remission at week 52 Secondary outcomes: • Mucosal healing at week 52 • Endoscopic remission at week 24 and 52 • Remission at week 24 and 52 • Remission without corticosteroids at week 24 and 52 and sustained remission without corticosteroids[31]
	Other outcomes • Remission at months 2, 12, 24 and 36 • Endoscopic healing of the colonic mucosa at months 2, 12, 24, and 3629	
IQWiG	**Comparators:** adalimumab, infliximab, golimumab or vedolizumab[32]	

When examining the comparators used on the phase III clinical trials for tofacitinib and those considered by the HTA agencies, it's noticeable that the agencies used a much wider range of comparators. In fact, CATS, SMC, HAS, and IQWiG selected the exact same comparators: adalimumab, infliximab, golimumab, and vedolizumab, while NICE in addition to those, select the conventional therapies as comparators. In contrast, the company only considered placebo as the main comparator for tofacitinib.

One more time is noticeable a more cautious approach from NICE regarding the selection of the population compared with the remaining agencies as it included not only biologic drugs but conventional therapy as well. It expresses the efforts in considering a wider range of options to be compared with tofacitinib in terms of effectiveness.

Differences and similarities in outcomes appear when comparing the company´s clinical trials and HTA agencies. Clinical remission is a common outcome in both induction and maintenance phases, deemed as a primary outcome by the company and HTA agencies. CATS and NICE, particularly, referred to clinical disease measures that encompass clinical remission and clinical response. This convergence underlines the importance of this outcome in assessing the therapeutic impact of tofacitinib in the treatment of UC.

All HTA agencies and the company reached a consensus in considering endoscopic and mucosal healing as a secondary outcome, which emphasizes the significance of these two parameters in measuring disease progression and treatment effectiveness. On the other hand, the assessment of quality of life using validated scales is considered a secondary outcome in almost all reports, except for the one made for SMC which, although acknowledging this aspect, did not classify it as an outcome.

Remission without corticosteroids is an outcome that is also considered by the company, HAS, and SMC, and apart from that, contrarily to the other HTA agencies. This aligns with the continuous effort in reducing reliance on corticosteroid therapy, thereby improving patient well-being.

Moreover, CATS and NICE consider rates of hospitalization and surgical intervention as outcomes, reflecting their focus on broader health system implications.

Ultimately, the company contemplates in the clinical trial two outcomes that are not selected by the agencies namely symptomatic remission and complete remission. The oversight of these outcomes by the HTA agencies may be assigned to specific reasons.

Regarding symptomatic remission, its exclusion could be related to its subjective nature, turning into a challenge quantifying it with consistency. Additionally, the assessment process related to this outcome might involve varying interpretations, leading to inconsistencies in the

evaluation. Furthermore, the lack of complete remission as an outcome selected by the agencies could be attributed to the clinical trials and their sample size. It's feasible that the clinical trials didn't encompass a sufficient amount and diverse patient population in order to comprehensively assess the possibility of achieving complete remission with tofacitinib.

As it happened in the assessment reports for ustekinumab, CATS, and NICE in addition to the efficacy outcomes, appointed some safety outcomes as well. CATS demonstrated a more comprehensive approach by assigning several safety outcomes, which rate them as critical and important. As critical were considered mortality, the incidence of adverse effects, discontinuation due to adverse effects, increased rate of opportunistic infections and infestations, and increased rate of neoplasms which indicates their commitment to understanding the treatment's impact on patients' wellness and the possibility of interrupting the treatment. Furthermore, selected as important safety outcome the overall incidence of adverse effects.

NICE approach to the choice of safety outcomes was more streamlined, and selected as safety outcomes, mortality, and adverse effects of treatment. This suggests that the agencies focused mainly on immediate and severe safety outcomes besides delving into a more comprehensive analysis of the overall impact of the treatment with tofacitinib.

The company didn't include in a formal why safety measures to be assessed, besides assessing the safety profile of tofacitinib. This can be translated into implications in the assessment reports, due to the lack of sample size in the clinical trial that can't guarantee a correct assessment of the safety measures defined by CATS and NICE.

It is important to note that the relative effectiveness assessment report from IQWiG is incomplete and the information about the outcomes chosen for tofacitinib isn't available, so it is only possible to make a comparison about the comparators.[32]

Number and type of studies included on the assessment reports by the HTA agencies

The HTA agencies to be able to draw a solid conclusion of the therapeutical evaluation had to rely on various studies and evidence sources.

CATS considered the study OCTAVE INDUCTION 1, OCTAVE INDUCTION 2 (both induction phase studies), and the OCTAVE SUSTAIN (maintenance phase study), as well as three NMAs provided by the company.[28] This suggests that CATS seeks to combine a variety of sources to achieve a more comprehensive understanding of tofacitinib's efficacy and safety.

NICE as well as SMC and HAS, besides the clinical trials evaluated by CATS, also considered the study OCTAVE OPEN (ongoing open-label long-term extension trial).[30; 31; 34] The reason behind this decision relies on the aim of seeking a more complete understanding of tofacitinib's performance over an extended period, its sustainability, and long-term effects. The integration of this ongoing trial demonstrates a wider perspective on the treatment's clinical effectiveness beyond the initial controlled trials made by the company to get acceptance by the different NHS.

While SMC didn't specify the number of the NMAs considered, NICE relied on two NMAs, and HAS didn't consider any direct or indirect comparison at all.

On the other hand, IQWiG took a more conservative approach to evidence selection since relied on much less evidence to draw its own conclusions, considering only the OCTAVE SUSTAIN trail, and didn't include any direct or indirect comparisons in its assessment report.[32]

In summary, these differences expose the uniqueness of the strategies used by the HTA agencies. Some of them leaned towards a more comprehensive data incorporation, including clinical trials and NMAs, while others showed a more focused approach, evaluating specific trial phases or long-term sustainability.

Conclusion of the therapeutical evaluation

The pharmacotherapeutic conclusions attained by the HTA agencies (CATS, NICE, SMC, IQWiG, and HAS) concerning tofacitinib for the treatment of ulcerative colitis reveal both differences and similarities.

CATS concluded that there is an indication of the comparability of tofacitinib with infliximab, adalimumab, vedolizumab, and golimumab in patients without and with previous exposure to biological agents. However, besides this comparability, CATS determined that as a result of the increased risk of pulmonary thromboembolism with tofacitinib, it should not be used in subjects that have never been exposed to biologic therapy[28]. CATS's pharmacotherapeutic conclusion is in line with its concern in assessing safety outcomes besides efficacy outcomes, something that not all agencies do. Moreover, it highlights the agency's prudent balancing between acknowledging tofacitinib's therapeutic comparability with the other treatment options while also addressing specific safety concerns, which underscores the importance of having a holistic assessment that deems both potential benefits as well as risks of treatment.

On the other hand, NICE acknowledged the added clinical benefit of tofacitinib compared to placebo in patients suffering from moderately to severely active UC. For people who have

not been exposed to anti-TNFα, due to indirect comparisons, NICE considered tofacitinib more effective than adalimumab and golimumab. When people experienced treatment with anti-TNFα, tofacitinib was only considered more effective than adalimumab, on the induction phase.[34] The committee recognized tofacitinib as a groundbreaking therapy due to its administration system (oral treatment) and its potentially less immunogenicity compared to biological agents because of being a small molecule.[34]

The oral administration method of tofacitinib differentiates it from the other biological agents that frequently require injections or infusions. The new feature could lead to enhanced patient compliance and convenience, impacting directly their quality of life. Along with this feature, NICE highlighting the potential for reducing immunogenicity compared to the other biologic agents underscores the therapeutic innovation that tofacitinib brings to the treatment landscape. The therapeutic decision made by NICE regarding tofacitinib expresses the importance of patient experience and immunogenicity for this agency.

SMC along with IQWiG, by analyzing the NMA provided by the company, recognized the comparability of tofacitinib in terms of efficacy. This affirmation suggests that tofacitinib has an important role and the ability to yield positive therapeutic outcomes in the treatment of UC. Moreover, these two agencies had the same opinion as NICE, stating that the administration method represents a huge advantage for this drug.

Despite all the advantages, SMC and IQWiG concluded that there is no available data that supports its superiority over the comparators analyzed. This prudent stance could be explained by the complexity of proving the superiority of a determined drug over its comparators, which can be justified by the need for comprehensive and robust clinical data showing clear advantages of one option over the other. The absence of such information could be associated with divergencies in the patient population studied, the trial design, and the range of the sample.[30; 32]

Lastly, HAS established tofacitinib as an alternative to vedolizumab in patients failing conventional treatment and anti-TNFα therapy and indicated that the choice between these two drugs must consider factors beyond efficacy, such as administration method and tolerance profile[31]. This recognition underlines the importance of adjusting the treatment decisions to individual patient needs, desires, and tolerances, showing a patient-centered approach to treatment recommendations.

Furthermore, they stated that there is no sufficient data available to consider tofacitinib superior to vedolizumab, that´s why they are in the same place. HAS also emphasized that tofacitinib has no place as a second line of treatment when patients have never received anti-TNFα therapy, due to the absence of a direct comparison between tofacitinib and the anti-

TNFα.[33] This judgment, aligns with the ones of the other HTA agencies mentioned above and follows the principle of evidence-driven decisions, making patient safety and treatment efficacy a priority.

As aforementioned CATS include in their assessment reports the overall quality of the evidence, and for this case, they considered that "the submitted evidence was considered moderate for the defined outcomes."[28] Categorizing the evidence as moderate, normally suggests that there are certain strengths in the studies, for example, adequate sample size or reasonable methodology, yet some limitations exist that hinder it from being considered high-quality or definitive evidence.

4.2 Crohn's disease

4.2.1 Ustekinumab (Stelara)

Therapeutic indication proposed for funding and considered in the SmPC

Furthermore, in addition to the formerly discussed medications used for UC, this study also included drugs indicated for Chron's disease, for which relative effectiveness assessment reports were conducted by CATS between May 2020 and the end of 2022.

Table 5 - Therapeutic indication considered on the SmPC and proposed for funding for ustekinuamb with indication for the treatment of DC.

Therapeutic indication considered on the SmPC for ustekinumab	
"STELARA is indicated for the treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies."[35]	
Therapeutic indication proposed for funding for ustekinumab	
CATS	"Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNFα antagonist or have medical contraindications to such therapies."[36]
NICE	"People with moderately to severely active Crohn's disease in whom the disease has responded inadequately to, or is no longer responding to, either conventional therapy or a tumour necrosis factor-alpha inhibitor, or who are intolerant to either of them"[37]
SMC	"Treatment of adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumor necrosis factor-alpha (TNFα) antagonist or have medical contraindications to such therapies."[38]
HAS	"STELARA is indicated for the treatment of moderate to severe active Crohn's disease in adult patients with insufficient response, loss of response or intolerance to conventional therapy or anti-TNFα or who have a medical contraindication to these treatments."[39]

Starting with the first one, ustekinumab, and analyzing its indication mentioned on the SmPC and comparing it with the ones proposed for funding by CATS, NICE, SMC, and HAS.

As evident from the table above, it can be observed that the therapeutic indication considered on the SmPC for ustekinumab aligns with the therapeutic indications proposed for funding by all HTA agencies. This congruence between indications signifies a collective acknowledgment of the drug's therapeutic scope. This alignment improves clarity for healthcare providers, guarantees consistent patient administrations, and highlights the shared understanding of ustekinumab's clinical use among regulatory and assessment authorities.

PICO considered in the phase III clinical trials and in the assessment reports

Regarding the analysis of the PICO chosen in the phase III clinical trials and comparing it with the one chosen for the HTA agencies, the starting point was the analysis of the population.

The inclusion criteria for the population to be included in phase III clinical trial were being an adult male or female diagnosed, at least for 3 months, with an active moderate to severe CD defined by a Chron's Disease Activity Index (CDAI) between 220 and 450, with confirmed colitis (inflammation of the colon), ileitis (inflammation of the ileum), or ileocolitis (inflammation of the ileum and colon) based founded on radiography, histology, and endoscopy.[35] These inclusion criteria was impelled by the wish to assess ustekinumab's efficacy and safety in a determined population that precisely mirrors the patients who would benefit from this treatment in real-world clinical practice.

The requisite for participants to be adult patients with active moderate to severe CD was fixed to assure that the study is orientated towards the therapeutic needs of subjects for whom the disease impact is substantial and requires intervention. Furthermore, defining the specific range of CDAI that should be included ensures that the clinical trials enroll patients with similar levels of disease activity, reducing confounding factors that could possibly impact the outcomes results. The reason behind the inclusion of patients with confirmed colitis, ileitis, or ileocolitis might be to ensure that the different manifestations of CD are being covered, helping in determining the drug's effectiveness across different disease exhibitions.

Additionally, were also considered subjects treated with infliximab, adalimumab, or certolizumab pegol at an approved dose for the treatment of CD, and these drugs didn't produce any response, produced response but subsequently lost response or showed to be intolerance in the subjects.[35] By including these subjects, a new layer of clinical relevance were added, and the trial besides trying to prove the effectiveness of ustekinumab, aimed to determine whether it could give a viable option for individuals who have failed the other treatment alternatives.

CATS, on its relative effectiveness assessment reports, considered 3 different populations: patients with moderate to severe active CD, who had an inadequate response, loss of response, contraindication, or demonstrated intolerance to conventional therapy (population 1), to anti-TNFα (population 2), and to all anti-TNFα (population 3).[36] The first population addresses a highly common scenario when standard therapies are shown to be unsuitable or ineffective which is considered a problem of the real world faced by clinicians and patients. The second and third populations represents a more advanced phase of the treatment resistance, where the patients have demonstrated a limited or negative response to a wide range of biological treatments, appointing for a more challenging clinical scenario.

This way, CATS embraced a broader perspective by sectioning the population into small groups based on treatment responses and intolerances, exhibiting that the final effort of CATS is to provide a more comprehensive acknowledge of ustekinumab's effectiveness across different scenarios of the disease. Also, separating into subpopulations allows CATS to evaluate the different outcomes within the different subpopulations.

In contrast to CATS, the other agencies, NICE, SMC, and HAS considered only one population: adult patients with moderately to severely active DC whom the disease has responded inadequately, lost response, or responded only in the beginning and then stopped, to either conventional therapy or anti-TNFα. Patients who are intolerant to such therapies were also included.[38; 39; 40] The other agencies by selecting a single population indicate a more standardized evaluation, which could be appropriate for some effectiveness assessments but for others might not catch the full complexity of the treatment in CD management.

Secondly, the comparators and outcomes selected by the company and HTA agencies were reviewed.

Table 6 - Comparators and outcomes considered in the phase III trials and considered by the HTA agencies for ustekinumab with indication for the treatment of DC.

<table>
<tr><th colspan="3">Comparators and outcomes considered in the phase III trials for ustekinumab</th></tr>
<tr><td colspan="3">Comparator: placebo[35]</td></tr>
<tr><td colspan="2">Induction phase outcomes
<u>Primary outcomes:</u>
• Clinical response at the end of week 6 [V]
<u>Secondary Outcomes:</u>
• Clinical remission at the end of week 8 [VI]
• Clinical response at the end of week 8
• 70-point response at the week 6 [VII]
• 70-point response at week 3[35]</td><td>Maintenance phase outcomes
<u>Primary outcomes:</u>
• Clinical remission at the end of week 44 [VIII]
<u>Secondary outcomes:</u>
• Clinical response at the end of week 44
• Clinical remission at the end of week 44 within subjects in clinical remission with ustekinumab at week 0
• Discontinuation of corticosteroid therapy at the end of week 44
• Clinical remission at the end of week 44 in subject's refractory or intolerant to anti-TNFα[35]</td></tr>
<tr><th colspan="3">Comparators and outcomes considered by the HTA agencies for ustekinumab</th></tr>
<tr><td rowspan="2">CATS</td><td colspan="2">Comparators: Infliximab, adalimumab, and improved medical and surgical supportive care[36]</td></tr>
<tr><td colspan="2">Outcomes
<u>Critical outcomes:</u>
• CDAI scores, with a minimum reduction of 70/100 points (relative to clinical response) or a total score <150 points (relative to clinical remission)
• Proportion of patients remaining in remission, free from corticosteroid use and surgery, for at least 12 months
• Minimization of the need for surgery
• Prevention of post-operative recurrence
• Fistula response
• Health-related quality of life assessed by validated scale
<u>Important outcomes:</u>
• Endoscopic markers: endoscopic changes and mucosal healing of lesions[36]
<u>Critical safety outcomes:</u>
• serious adverse events
• treatment discontinuation due to adverse events
• rate of opportunistic infections and infestations (or reactivation)
<u>Important safety outcomes:</u>
• rate of neoplasms[36]</td></tr>
<tr><td rowspan="2">NICE</td><td colspan="2">Comparators: conventional therapy (conventional corticosteroids alone or in combination with azathioprine, mercaptopurine or methotrexate, aminosalicylates, also budesonide alone or in combination with azathioprine, mercaptopurine or methotrexate), anti-TNFα (infliximab and adalimumab), vedolizumab[37]</td></tr>
<tr><td colspan="2">Outcomes measures to be considered
• Disease activity (remission, response, relapse)
• Mucosal healing
• Adverse effects of treatment
• Health-related quality of life[37]</td></tr>
<tr><td rowspan="2">SMC</td><td colspan="2">Comparators: Infliximab, adalimumab, and vedolizumab[38]</td></tr>
<tr><td colspan="2">Induction phase outcomes
• Clinical response at week 6
• Clinical remission at week 8
• Clinical response at week 8
• 70-point clinical response at week 3
• 70-point clinical response at week 6[38]</td></tr>
</table>

HAS	**Comparators:** Adalimumab, infliximab, and vedolizumab[39]	
	Induction phase outcomes Primary outcomes: • Clinical response at week 6 Secondary Outcomes: • Clinical remission at week 8 • Clinical response at week 8 • 70-points response at week 6 • 70-points response at week 3[39]	**Maintenance phase outcomes** Primary outcomes: • Clinical remission at week 44 Secondary outcomes: • Clinical response at week 44 • Clinical remission at week 44 among patients already in clinical remission at inclusion in IM-UNITI • Remission at week 44 without the use of corticosteroids • Clinical remission at week 44 in the subgroup of patients refractory or intolerant to anti-TNFα[39]

V Clinical response defined as a reduction from baseline in the initial CDAI score by >100 points. Subjects with an initial score between 220 and 248 are considered to have a clinical response.
VI Clinical remission defined as a CDAI score <150 points.
VII 70-point response defined as a reduction of more than 70 points from the initial CDAI score.
VIII clinical remission defined as CDAI score <150 points

Firstly, comparing the comparators selected by the company for the clinical trials of ustekinumab with those considered by the HTA agencies, we can identify both differences and commonalities. The company elected placebo as the comparator for ustekinumab, which differed from the comparator choices made by the HTA agencies[35] these could have been driven by the necessity of demonstrating ustekinumab superiority over a baseline control group, which usually is a common decision in the initial stages is the clinical development. However, choosing a placebo as a comparator doesn't give a direct comparison to other option treatments, which most of the time is an important criterion assessed by the HTA agencies.

In addition, infliximab and adalimumab are a common choice as comparators to all agencies, highlighting the main focus of the agencies on evaluating ustekinumab within a clinical context that mimics real world scenarios. Besides these two CATS decided that "improved medical and surgical supportive care" should also be a comparator but only for the population 3.[36] This decision reflects, the overall understanding made by CATS over CD that commonly evolves for a more severe treatment, which includes surgery after exhausting all treatment option, a perspective adopted only by CATS.

NICE, besides infliximab and adalimumab, considered vedolizumab and conventional therapy as comparators as well.[37] SMC and HAS considered exactly the same comparators, infliximab, adalimumab, and vedolizumab.[38; 39]

Furthermore, is important to note that NICE was the only HTA agency that considered as comparator the conventional treatment. This can maybe be explained by the aim of NICE in achieving a more comprehensive approach considering all the options since the conventional treatment is one of the first steps in the treatment of CD. On the other hand, the other

agencies immediately excluded conventional therapy as possible comparators, restricting ustekinumab only to a second line of treatment.

Analyzing the outcomes, it is possible to observe that clinical remission (complete absence of the symptoms) and clinical response (notable improvement in symptoms) are two outcomes with high prevalence in the assessment reports that are paramount to patients, clinicians, and decision-makers in reflecting the drug's impact in patients welfare. Some of them like the ones selected by SMC, HAS, and the company consider specific points in time (6, 8, and 44 weeks) to check the clinical remission and clinical response and the specific decrease in CDAI points. This carefully selection of the time points offers a structured technique for understanding the patient's response to ustekinumab across the different stages of CD. Moreover, establishing the specific decrease in CDAI points reflects the intention of the agencies and company to have a more quantitative and objective approach, since CDAI is considered a validated tool for assessing CD activity.

CATS and NICE don't specify as much as the other agencies in terms of time but CATS mentioned the necessary reduction in terms of CDAI score. The less specific approach in terms of time points might point that these agencies care more about the overall therapeutic effect rather than the short-term assessments since they didn't specify the exact time points of measure.

Discontinuation of corticosteroids, health-related quality of life, endoscopic changes, and mucosal healing are other outcomes selected by CATS, NICE, and HAS. Discontinuation of corticosteroids as an outcome is a huge milestone in the treatment progress of the disease, as it indicates the improvement of patients' long-term health by reducing the adverse event triggered by the excessive use of the corticosteroids. The decision to including health-related quality of life by the agencies also indicates their special attention to the impact of CD beyond clinical symptoms, as this is a highly debilitating disease that also impacts in emotional and social way the patient lives. Furthermore, endoscopic changes and mucosal healing were selected because these outcomes represent measures of the disease underlying pathology and its evolution.

CATS on the other hand presented some distinct outcomes such as: minimization of the need for surgery, prevention of post-operative recurrence, and fistula response, these outcomes don't appear in the assessment reports of the other HTA agencies nor on the EPAR. This selection once more emphasizes the preoccupation of CATS in having a proactive approach, trying to understand the possible impact of ustekinumab in some of the most severe and debilitating aspects of this disease, while being aware that a proven reduction of these

outcomes will not only impact in the patient well-being but also in the economic point of view for the NHS, due to high costs associated to surgeries and hospitalizations.

Besides the efficacy outcomes, CATS and NICE appointed safety outcomes. NICE didn't detail as much as CATS that selected as critical safety outcomes: serious adverse events, treatment discontinuation due to adverse events, rate of opportunistic infections and infestations (or reactivation), and as important safety outcome rate of neoplasms.[36; 37] Once more CATS and NICE, addressing safety outcomes besides the efficacy outcomes, show their interest in having a more holistic understanding of ustekinumab's impact on patients and willingness to achieve the overall benefit-risk balance.

Number and type of studies included on the assessment reports by the HTA agencies

In terms of studies, the HTA agencies ended up considering approximately the same studies. The UNITI studies were evaluated by all agencies and it consisted of a "multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III trial to evaluate the safety and efficacy of ustekinumab induction therapy (UNITI-1 and UNITI-2) and maintenance therapy (IM-UNITI) in patients with moderate to severe active Crohn's disease who have failed or are intolerant to TNF antagonist therapy".[35] The consistent incorporation of these studies on the assessment reports made by all HTA agencies indicates their importance in setting up the drug's effectiveness as well as safety profile.

In addition, a NMA comparing ustekinumab with anti-TNFα were considered by CATS35, and SMC considered different NMAs for both the induction and maintenance phase. [38]

NICE reviewed multiple NMAs for the induction phase and for the maintenance phase and considered a treatment sequence analysis instead of a conventional NMA.[40] The common decision to include NMAs in their assessments reveals the aim of setting the indirect comparisons between the different treatment options to achieve a full comprehensive evaluation. Besides this, NICE following a different path in assessing a treatment sequence analysis for the maintenance phases indicates their effort in not only assessing the indirect comparison but also the treatment's effectiveness in a specific sequence or order of therapeutic options.

Conversely, HAS made its considerations based in a retrospective observational study done by *Groupe d'Étude Thérapeutique des Affections Inflammatoires du Tube Digestif* (GETAID).[39] This divergence highlights HAS's attention to real-world data, which can lead to comprehensive insights into ustekinumab's effectiveness and safety in practical clinical environments.

Conclusion of the therapeutical evaluation

When comparing the conclusion made by the HTA agencies in terms of therapeutic evaluation, commonalities were found. All agencies' assessments of ustekinumab included the recognition of its comparability to other biological agents, particularly adalimumab and vedolizumab, which highlights the noticed effectiveness and position of ustekinumab amongst the available treatment options.

CATS for example, when assessing the additional benefit of ustekinumab, concluded about its comparability to adalimumab in people who failed both conventional and biological therapy[36], which suggests that ustekinumab can offer a similar level of therapeutic benefit compared with adalimumab on this specific subgroup (population 1 and 2). Additionally, stated that due to a limitation on the available data his use on people, who have failed to respond to all anti-TNFα[36], indicates reservations in the use of this drug in this particular subgroup (population 3). Again, this underscores that efforts must be made to reinforce the research in the area.

NICE made a balanced consideration regarding the ustekinumab use considering its efficacy, innovation, and cost-effectiveness. Firstly, they acknowledged ustekinumab as an innovative drug and equivalent in terms of efficacy to its comparators. Moreover, they consider that should be recommended for use in the NHS for treating moderately to severely active CD, but the choice between ustekinumab or another biological agent should be made taking into consideration a discussion about the advantages and disadvantages between the clinician and the patient. The less expensive treatment should be chosen when there is more than one treatment available.[40] NICE conclusion, therefore, underscores the need for a more patient-centered approach, always considering effectiveness and cost-effectiveness, with the purpose of giving optimal care and at the same time managing the healthcare resources effectively.

All HTA agencies agreed as well that ustekinumab could fulfill an unmet need in subjects who cannot tolerate or have contraindications to the use of anti-TNFα. Another example is SMC, that per the analysis of the NMAs found no evidence of a difference between ustekinumab and adalimumab, as regards people who failed conventional therapy, and between ustekinumab and vedolizumab or adalimumab on the portion of patients that experienced failure with treatment with anti-TNFα. Furthermore, SMC affirmed that infliximab appeared to be superior to ustekinumab as an induction treatment in the conventional therapy failure subpopulation.[38] This approach to evaluating ustekinumab within the different subpopulations shows the aim of SMC in filling up all the gaps in the treatment of CD.

HAS made their point stating that the actual benefit of ustekinumab is lacking in patients who are naïve to anti-TNFα and significant in patients who have failed the conventional treatment.[39]

Regarding the quality of the evidence, CATS rated as low for all outcomes, which indicates low certainty of the results, showing CATS reservations about the strength and reliability of the data.[36] Conversely, NICE considered that the information provided by the company, including the studies, was of good quality.[40]

This difference in assessing the quality of the evidence can be explained by the variations in the methodologies used by each HTA agency, expertise, and standards defined. It outlines how this divergency can impact and change the perspectives, and ultimately influence the assessment and recommendations.

4.2.2 Darvadstrocel (Alofisel)

Therapeutic indication proposed for funding and considered in the SmPC

Darvadstrocel was the last drug to be analyzed in this investigation, and it stands out as the only one with a distinct indication compared to the drugs studied earlier. The relative effectiveness assessment reports from CATS, NICE, SMC, and HAS were examined, and the first topic to be analyzed was the therapeutic indication considered on the SmPC and the one considered by the HTA agencies.

Table 7 - Therapeutic indication considered on the SmPC and proposed for funding for darvadstrocel with indication for the treating complex perianal fistulae recurrent of CD.

Therapeutic indication considered on the SmPC for Darvadstrocel	
"Alofisel is indicated for the treatment of complex perianal fistulae in adult patients with non-active/slightly active luminal Crohn's disease when the fistulae have shown an inadequate response to at least one conventional or biological therapy. Alofisel should only be used after conditioning of the fistulae."[41]	
Therapeutic indication proposed for funding for Darvadstrocel	
CATS	"Treatment of complex perianal fistulae in adult patients with non-active/slightly active luminal Crohn's disease when the fistulae have shown an inadequate response to at least one conventional or biological therapy. Alofisel should only be used after conditioning of the fistulae."[42]
NICE	"Adult with non-active/mildly active luminal Crohn's disease, with complex perianal fistulas which have shown an inadequate response to at least one conventional or biologic therapy."[43]
SMC	"For the treatment of complex perianal fistulae in adult patients with nonactive/mildly active luminal Crohn's disease, when fistulae have shown an inadequate response to at least one conventional or biologic therapy."43
HAS	"For the treatment of complex perianal fistulae in adult patients with non-active/mildly luminal Crohn's disease, when the fistulae have responded inadequately, to at least one conventional treatment or biologic therapy. Alofisel should be used after the fistulae preparation steps."44

The cross-analysis in terms of therapeutic indication for darvadstrocel (Alofisel) shows that all HTA agencies included in this analysis, concur on its general therapeutic use, with some slight differences, which almost perfectly aligns with the therapeutic use stated on the SmPC of darvadstrocel. This drug is used for the treatment of complex perianal fistulae that come due to the mildly/slightly or non-active CD. This consensus between the different agencies suggests their agreement on the population that could benefit from the drug. However, the slight differences can be explained by the distinct methodologies adopted for the different agencies, the way they prioritize certain subpopulations or the emphasis that they give on specific clinical criteria.

Additionally, all agencies agreed that its use should only be considered when the fistulae have shown an inadequate response to at least one conventional or biological therapy. This unanimous view suggests a joint recognition of darvadstrocel role as a secondary or specialized treatment option.

Moreover, CATS and HAS complemented stating that darvadstrocel should only be used after the fistulae preparation, which could be explained by the desire of the agencies to give more detailed guidance on the drug's optimal use, guaranteeing that it's used in a controlled and efficient manner.

PICO considered in the phase III clinical trials and in the assessment reports

Furthermore, the next topic analyzed was the PICO selected for the company on the phase III clinical trials for darvadstrocel within the indication under scope, and the PICO chosen by the HTA agencies.

The inclusion criteria for selecting the population for the phase III clinical trials were:

- "Individuals diagnosed with CD for at least 6 months, confirmed by clinical, endoscopic, histological, and radiological means;
- Individuals must have complex perianal fistulae, with a maximum of 2 internal openings and 3 external openings. The fistulae should have been drained for at least 6 weeks after study inclusion;
- Individuals must have failed treatment with at least one of the therapies, including antibiotics, immunosuppressants, or TNF antagonists."[41]

The cautious selection of the population for the clinical trials ensures a well-defined group that aligns with the target patient population for darvadstrocel future assessment.

The selection of the population for assessing the effectiveness of darvadstrocel, within the assessment reports vary across the HTA agencies. CATS in opposition to the other agencies

(NICE, SMC, and HAS) provided a more comprehensive breakdown of the population divided into three different subpopulations:

- "patients with non-active/mildly active CD, when complex fistulae with up to three external openings and up to two internal openings, have shown an inadequate response, loss of response, contraindication, or intolerance to conventional therapy" (population 1).
- "patients with non-active/mildly active CD, when complex fistulae with up to three external openings and up to two internal openings, have shown an inadequate response, loss of response, contraindication, or intolerance to anti-TNFα" (population 2).
- "patients with non-active/mildly active CD, when complex fistulae with up to three external openings and up to two internal openings, have shown an inadequate response, loss of response, contraindication, or intolerance to all anti-TNFα and α4ß7 integrin inhibitors" (population 3)[42].

CATS adopting a more comprehensive approach might be related to their intention to provide a more refined assessment of darvadstrocel's effectiveness in different situations and populations, with the objective of conducting a more nuanced assessment that aligns with the varied therapeutic journeys.

However, the other HTA agencies provided less detailed specifications compared to CATS, resulting in some differences in the chosen study population compared to the clinical trials. They included adult patients with non-active/mildly active luminal CD and complex perianal fistulas who had not responded adequately to either conventional or biological treatments.[43; 44; 45] These other agencies took broader criteria for the selection of the population and didn't specify the openings required to be selected or the biological therapies considered. Essentially, this selection could be associated with a desire for inclusivity and flexibility. By choosing less stringent specifications they get closer to real-world patients and scenarios.

Furthermore, this precise balance between specificity and generalizability it's extremely important. While CATS detailed their inclusion criteria, offering a more precise assessment for specific populations, this could restrain their findings and limit their external validity, on the other hand, the wider inclusion criteria selected by the other HTA agencies, might lead to more extensive results that could be more applicable to a wider group of patients.

In terms of comparators and outcomes proposed by the company in phase III clinical trials and the ones chosen by CATS, NICE, SMC, and HAS, the following table exposes them.

Table 8 - Comparators and outcomes considered in the phase III trials and considered by the HTA agencies for darvadstrocel with indication for the treatment of DC.

<table>
<tr><th colspan="2">Comparators and outcomes considered in the phase III trials for darvadstrocel</th></tr>
<tr><td colspan="2">Comparator: Curettage (surgical intervention) + placebo[41]</td></tr>
<tr><td colspan="2">Efficacy outcomes
<u>Primary outcomes:</u>
• Remission of perianal fistula in CD with absence of fistulae greater than 2 cm in size, as confirmed by magnetic resonance imaging, at the end of week 24
<u>Secondary outcomes:</u>
• Clinical remission (closure of all external fistulae) at the end of week 24
• Clinical response (closure of more than 50% of external fistulae) at the end of week 24
• Time to clinical remission/clinical response
• Relapse
• Time to relapse
• Changes in the Perianal Disease Activity Index (PDAI)
• Changes in quality of life using the IBDQ scale
• CDAI
• Van Assche Score (MRI based score of perianal fistulae)[41]</td></tr>
<tr><th colspan="2">Comparators and outcomes considered by the HTA agencies for darvadstrocel</th></tr>
<tr><td rowspan="2">CATS</td><td>Comparators: Best medical and surgical supportive care, infliximab, and adalimumab (population 1); Best medical and surgical supportive care and vedolizumab (population 2); best medical and surgical supportive care (population 3)[42]</td></tr>
<tr><td>Outcomes
<u>Critical outcomes:</u>
• Proportion of patients who remain in remission, with closure of fistulous tracts, as assessed by imaging evaluation, for at least 12 months
• Minimization of the need for surgery
• Health-related quality of life assessed by a validated scale[42]
<u>Critical safety outcomes:</u>
• serious adverse events
• the rate of opportunistic infections and infestations (or their reactivation
• the rate of neoplasms.[42]</td></tr>
<tr><td rowspan="2">NICE</td><td>Comparators: surgical management without darvadstrocel[43]</td></tr>
<tr><td>Outcomes measures to be considered
• Closure of fistula
• Recurrence of fistula
• Continence
• Mortality
• Adverse effects of treatment
• Health-related quality of life[43]</td></tr>
<tr><td rowspan="2">SMC</td><td>Comparators: control treatment (surgical EUA +/- seton placement plus curettage)[44]</td></tr>
<tr><td>Outcomes
<u>Primary outcomes:</u>
• Combined remission at week 24 [IX]
<u>Secondary outcomes:</u>
• Clinical remission at week 24
• Clinical response at week 24 [X]
• Time to clinical remission at week 24 [XI]
• Time to clinical response at week 24
• Relapse of clinical remission by week 24[44]</td></tr>
</table>

HAS	**Comparators:** infliximab and its biossimilars, adalimumab, local surgery and diversion surgeries and proctectomy[45] **Outcomes** <u>Primary outcomes:</u> • The proportion of patients achieving remission at week 24 <u>Secondary Outcomes:</u> • Remission and clinical response at week 24[45]

IX Combined remission defined as closure on clinical assessment of all external openings that were draining at baseline and absence of collections >2 cm of the treated perianal fistulae in at least two of three dimensions confirmed by centrally reviewed MRI images

X Clinical response defined as closure equal or superior to 50% of external openings

XI Clinical remission defined at any previous visit as reopening of any of the treated external openings with active drainage as clinically assessed or development of a >2 cm perianal collection of the treated perianal fistulas confirmed by central MRI assessment

As highlighted in the table above, the different HTA agencies selected various comparators to assess the effectiveness of Darvadstrocel in treating complex perianal fistulae caused by CD. In their phase III clinical trials, the company selected a surgical procedure (curettage) plus placebo as the main comparator.[41] Curettage, is a surgical procedure commonly used for managing complex perianal fistulae[46] and for this reason, represents a relevant benchmark for the assessment of the potential benefits of darvadstrocel. The choice of the company to including a placebo on the other arm might be justified by the aim to isolate the specific effects of the study drug, and to show its efficacy, considering that the phase III clinical trials are very important for obtaining the marketing authorization and acceptance.

However, the agencies opted for other comparators, such as infliximab, adalimumab, and vedolizumab. Despite these variations, all agencies selected surgical procedures as a common comparator.[42; 44; 45; 47] This selection of comparators, reflects the agencies' tendency to evaluate darvadstrocel effectiveness, considering all contexts of established therapeutic alternatives that are orderly used in real clinical practice.

CATS decided that "best medical and surgical supportive care" should be chosen as the comparator for population 3. For populations 1 and 2, this comparator was paired with infliximab, adalimumab, and vedolizumab, forming two different groups. CATS was the only HTA agency that linked different comparators to specific populations[42], which aligns with CATS's concern in adopting a tailored approach that attempts to provide the best comprehensive insight into darvadstrocel effectiveness across multiple scenarios and shows their commitment to directing assessments that reflect real-world clinical practice and patient's needs.

Apropos of outcomes, commonalities can be found. Clinical remission/response at week 24 is a common outcome to both the company and the HTA agencies, as well as time to clinical remission and response, and health-related quality of life. These outcomes were selected because are considered universally key indicators of therapeutic efficacy and patient

welfare, these are more likely to give essential information on darvadstrocel impact on CD activity and patient's overall quality of life.

Some outcomes, such as relapse, time to relapse, and changes in the PDAI, CDAI and Van Assche Score were specific to phase III clinical40. These outcomes, besides reflecting the drug's effectiveness, sustainability of the treatment response, and disease intensity, they were not common choices among the HTA agencies, and this could be explained by the variations in the sense of relevance of these outcomes through healthcare systems.

CATS and NICE were the only two agencies that went across a more detailed selection of outcomes like minimization of the need for surgery, closure, recurrence of the fistulae, and continence.[42; 43] As we've become accustomed to throughout this analysis, CATS and NICE opted for a more holistic understanding, as these outcomes reflect the clinical and practical aspects of patient's lives above mere disease activity.

Furthermore, in the CATS relative effectiveness assessment reports, safety outcomes were also taken into consideration. The critical safety outcomes focused on serious adverse events, the rate of opportunistic infections and infestations (or their reactivation), and the rate of neoplasms.[42]

Similarly NICE, in alignment with CATS, also prioritized safety outcomes in their evaluation. The safety outcomes considered by NICE included mortality and adverse events related to the treatment.[43]

The selection of these safety outcomes showcases the agencies' dedication to safeguarding the patient's well-being while evaluating the effectiveness side of the therapeutic intervention keeping in mind a wider healthcare landscape.

Number and type of studies included on the assessment reports by the HTA agencies

The HTA agencies guided their assessment reports on the effectiveness and safety of darvadstrocel by considering fewer studies than usual, and none of them considered either direct or indirect comparisons. CATS, SMC, and HAS considered the ADMIRE-CD study – "a phase III, randomized, double-blind, parallel-group, placebo-controlled, multicenter study" – that took place over 24 weeks and had an extended follow-up period of 104 weeks.[41; 42; 44; 45]

This choice of not considering any comparisons might stem from the robustness of the study analyzed. In some cases, when an agency considers that the study is well-design and well structured, and aligns perfectly with the scope of the evaluation, the HTA agencies may

prioritize the deep analysis of this study in the deterioration of spending their resources in analyzing sources of indirect and direct comparison.

NICE, also based its analysis on the study ADMIRE-CD, and in addition considered a study from St Mark´s Hospital, located in London, because deemed that the original study provided by the company didn't include people from the United Kingdom.45 By considering, this last mentioned study, NICE was able to ensure an important representation of the local population and their needs, enabling a more comprehensive assessment of darvadstrocel therapeutic use.

Conclusion of the therapeutical evaluation

On the therapeutical evaluation of darvadstrocel for the purpose of public funding for the treatment of complex perianal fistulae in adult patients with non-active or mildly active luminal CD, when the fistulae had shown an inadequate response to at least one conventional and biologic treatment, CATS considered that, in comparison with its comparators, darvadstrocel showed an indication of added therapeutic value, though not quantifiable. Besides that, the added value could not be evaluated in populations 1 and 3, while for population 2, there were no possible indirect comparisons considering only the ADMIRE-CD study due to significant differences between the study population and the one under evaluation. Moreover, CATS stated that no significant safety issues were identified with the use of darvadstrocel, due to this its use was accepted in a hospital setting in Portugal.[42]

Regarding the quality of the evidence, CATS considered as moderate.[42]

It can be considered that CATS took a leap of faith in accepting darvadstrocel within the NHS because the therapeutic added value prevailed over the challenge of quantifying it.

NICE was more septic regarding the use of darvadstrocel and concluded that it is not recommended within its indication, due to reservations about the clinical effectiveness. Also, stated that has only a modest benefit over placebo and that the duration of its benefit remains uncertain due to the short period of time covered for the data available. As aforementioned, NICE considered the study ADMIRE-CD to make their considerations, and they assessed that the trial excluded individuals with the most severe and simplest fistulae, limiting its potential benefit for multiple complex fistulae due to volume restrictions for darvadstrocel administration45. This highlights the different priorities of each agency regarding the benefit and applicability to specific populations, and in this case, NICE had a more conservative approach compared to CATS.

Contrary to CATS, SMC also did not recommend darvadstrocel for use within NHSScotland due to several reasons. Firstly, the SMC opinion is that the phase III clinical trials

did not exhibit statistically significant differences between darvadstrocel and placebo in terms of health-related quality-of-life measures. Also, there is no proof to support the reduction of infections, maintenance of fecal continence, or decrease in the number of patients requiring surgery with the use of darvadstrocel. Furthermore, SMC defends that the implications for the healthcare service because of its administration and patient preparation, as well as staff training, were not properly addressed by the submitting company's analysis.[44] In summary, SMC was much harsher in their assessment, criticizing darvadstrocel's clinical effectiveness safety, and practical implementation, showing that they had a broader perspective of the overall impact of the drug implementation on the health care system.

HAS as well as SMC and NICE, issued an unfavorable opinion on granting marketing authorization for darvadstrocel in France. They highlighted that the clinical data in terms of efficacy, couldn't be considered, due to be based on a pivotal study, with only a marginal effect size compared to placebo, and has no further confirmation from previous studies. In addition, they considered the moderate effect size, short follow-up, safety data, and lack of data in patients requiring additional injections important key points that lead to the darvadstrocel not being recommended. In conclusion, the committee concluded that Alofisel is not suitable after failure or inadequate response to conventional treatments alone and is unlikely to offer significant public health benefits.[45]

In conclusion, darvadstrocel is the perfect example of how the discrepancies in the assessments made by the different agencies, can impact their final decision. Each one, weighed different factors such as clinical effectiveness, safety, evidence quality, and practical implications, leading to unique perspectives, priorities, and ultimately recommendations.

5 Limitations

While conducting my research, I was confronted with several limitations that warrant careful consideration.

One of the primary limitations arose from the inconstant level of data detail in the reports made by the different HTA agencies. The extent of information provided, displayed a significant degree of variability, especially in the description of the studies analyzed. In the majority of the reports, the agencies were rather vague in presenting the information on which their assessment was founded. This variation in the depth of reporting may have impacted not only the precision of my analysis but also its overall accuracy as well. It probably led to an incomplete understanding of certain nuances and could have introduced biases into my conclusions.

The absence of clear and comprehensive information regarding the NMAs assessed by the agencies showed up to be a huge limitation introducing ambiguity or compromising the robustness of my conclusions.

Furthermore, another limitation appeared during the analysis of the assessment reports made by the IQWiG. The reports from IQWiG were particularly incomplete, hindering a clear comparison and examination of their results, aside from the other agencies. This incompleteness could lead to a skewed interpretation of the whole results and conclusions.

6 Conclusion

The extent analysis of the effectiveness assessment reports from the most prominent agencies in Europe, regarding ustekinumab, tofacitinib, and darvadstrocel within the treatment of Crohn's disease and ulcerative colitis has clarified some significant nuances that form their respective evaluations.

Particularly, CATS and NICE stand out for their continuous effort in enhancing the safety outcomes, acknowledging the primary importance of patient welfare beyond mere measures of the disease activity. They repeatedly acquired a holistic approach which reflects in a wider impact of these therapies in patients' lives. Moreover, this highlights their dedication to considering the overall patient experience.

In contrast, SMC and HAS tended to guide their reports accordingly to the boundaries defined for the phase III clinical trials, aligning their defined outcomes with the trial-defined ones. This approach possibly limits their capacity to capture the full scope of treatment's impact, particularly those aspects, like patient quality of life and resources impact, that extend beyond the clinical trials settings. Sometimes, the rigidity and simplicity of their focus could restrict their ability to appreciate the real-world effectiveness of the assessed drugs.

An important aspect to address is the fact that CATS emerged as the sole agency to support the use of darvadstrocel, underscoring the diverged evaluation process across the different agencies and showing CATS's unique perspective on darvadstrocel therapeutic value within their specific healthcare context. Besides darvadstrocel, in the other assessments, the conclusions were mostly unanimous across the agencies, which indicates the joint effort in standardizing the methodologies used across the European HTA agencies.

Furthermore, Infarmed adopted the GRADE system to assess the quality of the evidence, something that wasn't adopted by the other agencies. This decision demonstrates the agency's commitment to a strict and standardized evaluation process, promoting transparency and reproducibility in their assessment reports.

Collectively, this research underlines the discrepancies and commonalities of the multiple factors in the evaluation of new technologies for UC and CD. The discoveries underscore the ultimate importance of the agency's specific priorities, methodologies, and considerations, that in the last instance collectively shape the ultimate recommendations, provide the best and most reliable evidence to the stakeholders, and lastly ensure optimal patient care.

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