NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Baricitinib for treating severe alopecia areata [ID3979]

Summary of Information for Patients (SIP)

August 2022

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Summary of Information for Patients (SIP):

The pharmaceutical company perspective

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Generic name: baricitinib; **brand name**: Olumiant®

1b) Population this treatment will be used by:

Please outline the main patient population that is being appraised by NICE:

The population that this treatment will be used for is **adult patients with severe alopecia areata (AA)**.

1c) Authorisation:

Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

The **Medicines and Healthcare products Regulatory Agency** (**MRHA**) is reviewing whether baricitinib should be approved and granted **marketing authorisation** as a treatment for adult patients with severe alopecia areata (AA). The **marketing authorisation** for baricitinib is therefore pending. More information on this can be found in **Document B** in **Section B.1.2**.[a]

[a]Please note that further explanations for the phrases highlighted in **orange** are provided in the glossary (**Section 4b**). Cross-references to other sections are highlighted in **green**.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Lilly are currently working with Alopecia UK to develop a sponsorship agreement to support disease awareness activities.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England. Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

The main condition that baricitinib plans to treat is alopecia areata (AA)

What is AA?

AA is a skin condition that causes sudden hair loss, usually in small, round patches. In most people, AA affects the scalp, but sometimes hair loss can occur on other parts of the body such as the beard, eyebrows and eyelashes.[1,2]

What are the different types of AA?

The hair loss in AA can be very different between different people. Some people may only have a few small patches of hair loss on the scalp. Other people have complete hair loss on the scalp or on the entire scalp and body.[3] Hair loss can also occur in different patterns, such as on certain parts of the scalp or body.[4] Sometimes, people with AA may also have changes to the appearance of their nails, with multiple pits or ridges forming.[3]

The appearance of the different types of AA are explained in **Table 1**.

Table 1. Types of AA[4]

Type of AA	Appearance
Patchy AA	One or multiple patches of hair loss on the scalp
Alopecia totalis	Complete loss of hair on the scalp
Alopecia universalis	Total loss of all body hair, including the scalp
Ophiasis	Hair loss on the sides and lower back of the scalp
Ophiasis inversus (sisapho)	Hair loss in the centre of the scalp
Diffuse/AA incognita	Thinning of hair all over the scalp
Alopecia barbae	Patches of hair loss in the moustache or beard

What is different about severe AA?

People with severe AA have hair loss that affects a larger area of the scalp. This can include:[5]

- People who have complete hair loss on the scalp (**alopecia totalis**)
- People with complete hair loss on the scalp or body (**alopecia universalis**)
- People who have large and/or many patches of hair loss that affect a large overall area of the scalp (**patchy AA**)

Sometimes, a special measurement is used to assess how much (or the 'extent') of hair loss a patient has, called the **S**everity of **Al**opecia **T**ool, or **SALT**. The **SALT** is used to calculate a patient's **SALT score**, which describes the percentage of hair loss that a patient has on their scalp. A **SALT** score of 0 means that a patient has no hair loss, and a score of 100 means that the patient has complete loss of their hair on the scalp.[6,7]

Even though there is no formal or universal definition of severe AA, someone with a **SALT** score of **50 or more** (indicating more than 50% hair loss) is generally considered to have

severe AA.[5] **SALT** scores may be used by a doctor to determine the best management for AA.[4] They may also be used in **clinical trials** to determine how well a treatment is working.[7,8]

What causes AA?

AA is an **autoimmune disease**, which means that a patient's own **immune system** mistakenly attacks the **hair follicles**. Because of this, the **hair follicle** becomes inflamed, which eventually makes the hair fall out. The reason for this attack on the **hair follicle** is not fully understood. It is also not known why only certain areas are affected.[9]

How does AA progress over time?

AA is **non-scarring**, which means that there is no permanent damage to the **hair follicle**. This means that new hair can grow back in the affected areas.[3] However, it is difficult to predict how AA will progress over time.[6] In around 80% of people with mild **patchy AA**, the hair regrows on its own (or 'spontaneously') without treatment in about a year.[10] However, people will often experience multiple episodes of hair loss during their lifetime.[1] In addition, around 1 in 4 people with mild AA will progress to having more severe hair loss.[3]

In people with severe AA, especially those with severe hair loss from the beginning, hair rarely regrows spontaneously.[1,6] Studies show that only around 1 in 10 people with **alopecia totalis** or **alopecia universalis** recovered after 5 years with or without treatment.[11] Patients who have AA from a young age, patients with nail changes and people with other **autoimmune diseases** also have a lower chance of recovery.[6]

How many people get AA?

In the UK, AA affects approximately 15 in every 10,000 people.[12] Experts have estimated that patients with severe AA make up around 10–30% of these people.

AA affects both men and women equally and can occur at any age. However, AA occurs more often in younger people. People with AA usually start showing symptoms of AA between the ages of 25–29 years old.[13]

What is the impact of AA (disease burden)?

Physical impact

The hair loss that occurs due to AA does not normally cause physical symptoms, but some people may have some itching, tingling or burning before or while the hair falls out.[14] However, if AA causes eyelashes and eyebrows to fall out, then the eyes may become sore due to dust, particularly in dry and windy conditions. This is because the protective function of the eyebrows and eyelashes is lost. Some people with AA may also get more sunburnt as the hair is not able to protect the skin from the sun like it usually would.[15]

Emotional impact

AA can be very upsetting for patients, as hair plays an important role in a person's identity and self-worth.[3,16,17] Certain cultures may also view hair as being sacred.[18] Because of this, AA can affect a patient's self-esteem, body image and confidence. AA can therefore cause patients to experience feelings of shock, trauma and loss of identify.[19,20] As the hair loss is often very visible, patients may also feel judged by other people.[21]

AA can also be very stressful for patients because the hair loss is unpredictable.[13,20] Some patients may find it very difficult to cope with their disease worsening after a period of improvement or if new patches of hair loss appear while others start to regrow.[22] If AA doesn't improve for a long time or gets worse, some patients may also begin to feel hopeless.[20]

Mental impact

As AA can be very upsetting and stressful, patients with AA have a higher chance of suffering from anxiety and depression than people without the condition.[3,19] In one study including 388 people with mild and severe AA in the UK:[19]

- 37% suffered from social anxiety
- 35% suffered from anxiety and
- 29% suffered from depression

Impact on quality of life

AA usually has a negative effect on patients' **quality of life** because of the emotional and mental impacts of the disease. Many studies have shown that compared with the general population, patients with AA have a lower **quality of life**.[23-25] In fact, patients with AA have a similar **quality of life** to people with other skin conditions that cause itching or poor sleep, even though AA does not usually cause serious physical symptoms.[25]

Patients with severe AA usually have a lower **quality of life** compared to people with milder AA.[24-26]

Impact on employment and relationships

Some people with AA find it difficult to go to work due to the mental and emotional impact of AA.[17,21] People with AA are therefore more like to have time of work or remain unemployed after being diagnosed with AA.[27]

AA can have a negative effect on a person's social life and relationship with their friends, family or partner. For example, some people with AA feel that they cannot start a romantic relationship, while others may experience the end of a relationship because their partner was not able to cope with the hair loss.[20] People with AA may also avoid social situations. One study including people with either severe or mild AA found that more than half avoided social situations or avoided seeing their friends because of their condition.[28]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

How is AA diagnosed?

The diagnosis of AA is based upon the appearance of the hair loss and if other causes of hair loss have been ruled out.[6] Other things which doctors look for are:[7]

- Short hairs, broken off a few millimetres from the scalp which are usually at the edges of patches of hair loss. These are sometimes referred to as "exclamation point hairs".
- Whether the hair can be easily pulled out, which suggests that the hair is falling out (or “shedding”). This can be checked by using a pull test, where a doctor holds approximately 40 to 60 hairs and gently pulls them away from the scalp.

Usually, more tests are not required after a doctor has examined the patient’s hair loss and asked about a patient’s medical history. However, sometimes further tests can be useful to rule out other causes of hair loss which may look similar to AA. Other tests that may be used include **trichoscopy** and **histopathology**, which are used to look more closely at the hair and scalp for signs of AA.[3]

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.

Please also consider:

  - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
  - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

What are the current treatment options for AA?

At the moment, there are few treatments which are approved for AA. Because of this, many treatments for AA do not have approval by the **MRHA** to be used for patients with AA (they are used "**off-label**"). This means that there is a lack of strong evidence from **clinical trials** to show whether or not these treatments are effective when used for AA. Because of this, many treatments for AA may not work at all, or only work for a short period of time. Some of these treatments also cause **side effects** which are uncomfortable or unpleasant for patients.[6]

The different treatment options that may be used for patients with AA are explained in more detail below. The aims of treatment are to:[5]

- Make the hair regrow and stop further hair loss from happening
- Improve a patients' **quality of life**
- Limit **side effects** that may be caused by treatment

"Watch and wait"

Watch and wait is when a patient does not receive treatment for their AA immediately after diagnosis, and instead is monitored closely by their doctor for signs of hair regrowth. Watch and wait is a common option for patients after being diagnosed with AA. This is because some patients will spontaneously recover, especially patients who have milder forms of the condition. In these patients, it may not be worth the patient experiencing the potential **side effects** of treatment if they are likely to recover without treatment.[6]

Unfortunately, those with severe AA rarely spontaneously recover, so will often have no regrowth or further hair loss.[6,22] Various other treatment options may be tried in these patients, which are explained in more detail below.

Topical steroids

Steroid creams or gels that are applied to the scalp (**topical** steroids) may help the hair regrow. However, there is little strong evidence which shows that this treatment is effective in patients with AA. Often, **topical** steroids do not cause any or lasting hair regrowth, especially in patients with severe AA.[6,22] This treatment can also cause a painful side effect called **folliculitis**, where the **hair follicle** becomes inflamed.[3,6]

What are steroids?

Steroids are a type of medicine which reduce inflammation. In theory, they can therefore help to reduce the inflammation that happens in the hair follicle and so can help to make the hair regrow in patients with AA.

Intralesional steroids

Intralesional steroids involve a doctor injecting **steroids** (about 1 cm apart) into the scalp where there are patches of hair loss. Studies have shown that **intralesional**

steroids can cause tufts of hair to grow at about 60–67% of injection sites.[13] However, the hair regrowth is only temporary, so injections are needed every 4 to 6 week in order for a patients to experience continued hair growth. Unfortunately, having these injections often can lead to **side effects** such as skin thinning and patches of skin that are lighter than the patient's normal skin tone (hypopigmentation). They can also be very painful and uncomfortable for patients. Due to the number of injections that would be needed for large areas of hair loss, this treatment is also not recommended for patients with severe AA.[6]

Steroid tablets (oral steroids)

Steroid tablets are another option that may be tried in patients after or during treatment with **topical steroids**. Some patients may experience some hair regrowth after taking oral steroids, but usually when the treatment stops, the hair loss comes back.[29] The hair regrowth that may occur with **oral steroids** is also often not worth the **side effects** of this medicine, especially when they are taken over a longer period. Side effects include raised blood pressure, **diabetes**, **stomach ulcers**, **cataracts** and **osteoporosis** as well as weight gain.[6,13]

Topical immunotherapy

It is thought that topical immunotherapy is the most effective option for people with severe AA. However, only around 20–30% of people with AA respond to this treatment. Topical immunotherapy involves putting a substance on the affected skin to make the skin react. This skin reaction affects the process involved in causing AA, and therefore allows the hair to regrow. A commonly used substance for topical immunotherapy is a drug called diphenylcyclopropenone (DPCP).[6]

Unfortunately, topical immunotherapy causes some unpleasant and painful **side effects**, such as severe skin reactions. This treatment is also not consistently available in the UK because it is a specialised treatment that can only be given in some hospitals.[6]

Other

Some other treatments that have been used in patients with AA include:

- **Ultraviolet light treatment (PUVA)**
- **Immunosuppressant** tablets

However, these treatment have very limited evidence that shows that they are effective in patients with AA, so they are not normally recommended.[6]

Wigs:

Patients with severe AA have hair loss that is extensive on the scalp, which is very visible to others. Some patients may therefore attempt to cover their hair loss with a wig. Wigs can help patients cope with the mental and emotional impact of AA, but some patients may feel self-conscious about wearing a wig for fear of being discovered.[6,22]

Psychological support:

Some people with AA may find it necessary to have **psychological support** to help them cope with their hair loss. This can include contacting support groups, or talking to a

psychologist or other doctor that has experience in helping patients cope with their mental health.[3,6,13]

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

AA from the patient perspective

AA can be a very difficult condition for people to cope with and can impact many areas of a patient's life. In particular, the emotional and mental impact of AA can make it hard to carry out day-to-day activities, socialise, and perform at work. In patient interviews, there were some parts of daily life which patients commonly mentioned were affected by AA. These included:[15]

- **Emotional impact:** Many participants with AA reported that the loss of their hair was "traumatic" and that it had a large impact on their self-confidence, self-esteem, and sense of self-worth. One patient said that AA "changed my life, my mind, and my heart. It made me weak and vulnerable, battered my self-esteem, and heightened my insecurities" and that they would "give anything to get my hair back"'. Several participants said that they had experienced depression because of their AA.

- **Stigma and social isolation:** Many of the participants explained that they had experienced stigma and isolation, such as bullying or being misunderstood by others. For example, one participant said "I spent many years in constant fear of being discovered as a bald woman, fearing being thought of as sick, bizarre, ugly, or worse."

- **Relationship impacts:** Participants explained that they often had trouble finding and maintaining personal and romantic relationships, and some even called this one of the biggest effects of AA for them. One patients said she was "living in fear of being rejected, not found to be attractive, unfeminine".

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities. If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.
Baricitinib belongs to a group of medicines called **Janus kinase inhibitors**. This means it works by blocking the action of a **protein** inside the cell known as **Janus kinase**. These **proteins** play an important role in the inflammation and damage that occurs in AA that cause hair loss. By blocking these **proteins**, baricitinib reduces inflammation in the **hair follicle** and therefore causes the hair to regrow.[30,31] In this way, baricitinib treats the underlying causes of AA and is therefore an innovative new treatment option for patients with AA. Another resource that has further information on how baricitinib works is the Patient Information Leaflet (Package leaflet: Information for the patient | Olumiant).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines? • Yes / No If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together. If yes, please also provide information on the availability of the other medicine(s) as well as the main side effects. **If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.**
Baricitinib is not intended to be used with any other treatment for AA.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for. How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

How is baricitinib taken?

Patients take baricitinib once a day as a tablet. Patients should swallow the tablet with a drink of water. Baricitinib can be taken with or without food.[32]

As baricitinib is taken as a daily tablet, patients can have their treatment at home or at work. This may be more convenient for patient as they don't have to go to the hospital or the doctors to receive their treatment, unlike some other AA treatments.[32]

How much medicine do patients take and when?

Most patients will take a tablet containing **4 mg** baricitinib. Some patients may take a lower dose of 2 mg once a day, but this may only be used for patients who are older than 75 years or if they have a high risk of infections. If the medicine is working well, a patient may also be given a lower dose of 2 mg baricitinib.[32]

Baricitinib tablets should be taken at the same time every day, if possible. If a patient forgets to take baricitinib, they should take the tablet as soon as they remember on the same day. The next dose should then be taken at the usual time on the next day. Patients should not take two tablets at the same time to make up for any missed doses.[32]

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Studies of baricitinib in AA

Two clinical trials have studies baricitinib for the treatment of adult patients with severe AA. They are called **BRAVE-AA1** and **BRAVE-AA2**.

Both BRAVE-AA1 and BRAVE-AA2 were **Phase 3 trials**. This means they looked at how well baricitinib worked to treat AA (its **efficacy**) and how safe the medicine was compared to the standard treatment. Both trials also looked at the impact of baricitinib on patients' **quality of life**.

In BRAVE-AA1 and BRAVE-AA2, baricitinib was compared to a **placebo**. Patients therefore received one of the following three options:

1. Placebo (equivalent to watch and wait)
2. 2 mg baricitinib
3. 4 mg baricitinib

These studies included patients with **severe AA**, which meant patients:

- Had a current episode of AA lasting for longer than 6 months, where hair loss was affecting more than 50% of the scalp (**SALT** score of greater than or equal to 50)
- Had not had any spontaneous improvement over the past 6 months
- Had not suffered from their current episode of AA for longer than 8 years (or if it was longer than 8 years, had experienced some periods of hair regrowth)

A summary of the key information about each trial is provided in **Table 2**.

Table 2. Trials investigating baricitinib

Trial name and number	Location	Number of patients included	Expected trial completion date
BRAVE-AA1	International: 70 sites across 3 countries (United States, South Korea, and Mexico)	654	June 2024
BRAVE-AA2	International: 98 sites across 9 countries (including the United States, Argentina, Australia and Brazil)	546	May 2024

More information about BRAVE-AA1 and BRAVE-AA2 can be found here:

- King B et al, 2022. (https://pubmed.ncbi.nlm.nih.gov/35334197/)
- ClinicalTrials.gov (BRAVE-AA1) (BRAVE-AA2)

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is

compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Trial results

In the BRAVE-AA1 an BRAVE-AA2 studies, the **efficacy** of baricitinib was measured according to how well it improved 3 key things after 36 weeks of treatment:[33]

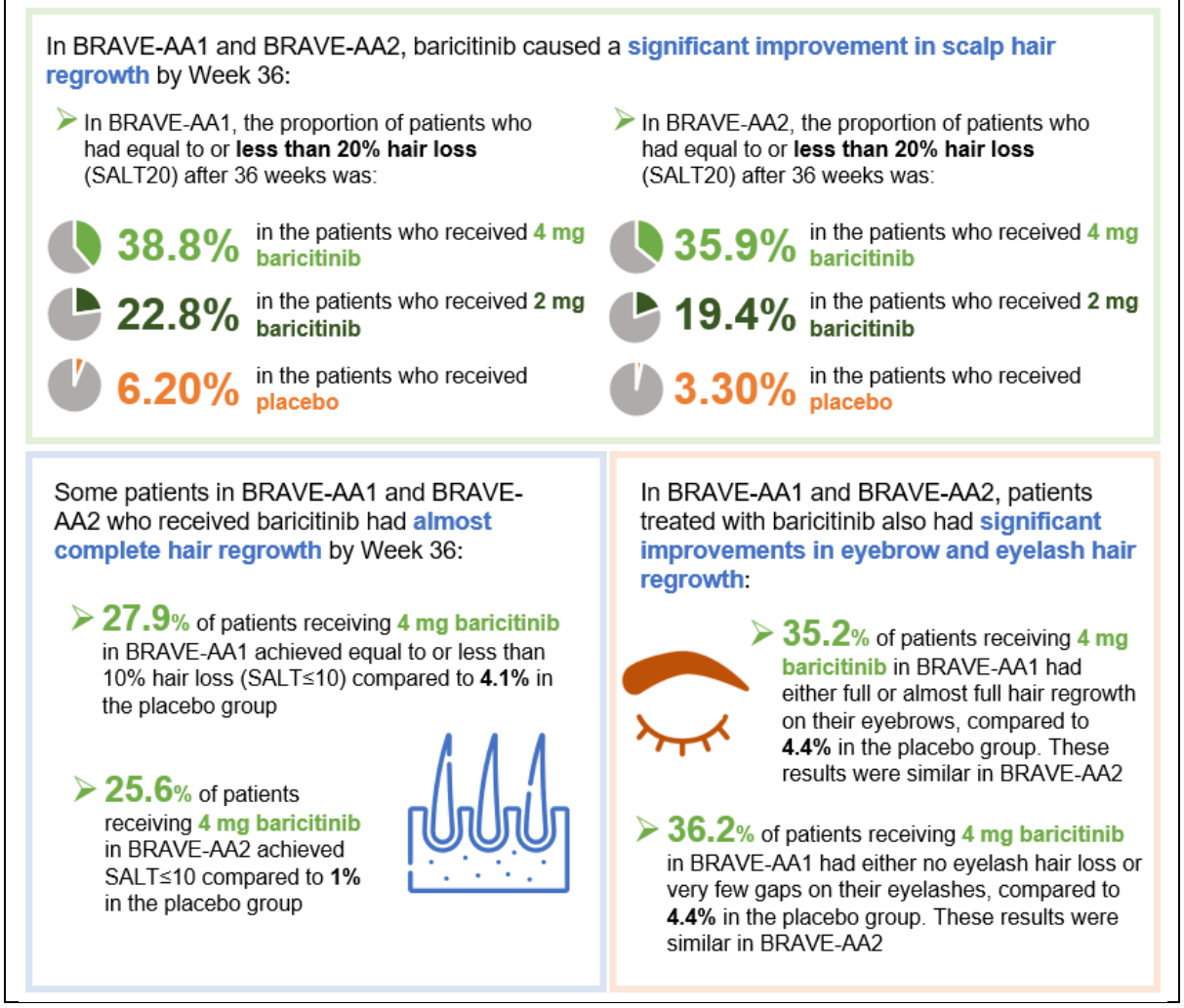
- **Scalp hair regrowth**: this was measured by looking at how many people achieved a particular **SALT** score. The **SALT** scores that were measured showed different levels of improvement compared to the beginning of the trial, where all patients had equal to or more than 50% hair loss.

- **Eyebrow hair regrowth**: this was measured using a scale from 0 to 4, where a score of 0 indicated that there was full or nearly full eyebrow hair coverage on the eyebrows, and a score of 4 indicated that there was nearly no or no eyebrow hair.

- **Eyelash hair regrowth**: this was also measured using a scale from 0 to 4, where a score of 0 indicated that there was full or nearly full eyelash hair coverage, and a score of 4 indicated that there was nearly no or no eyelashes.

Figure 1 shows the key efficacy results of the BRAVE-AA1 and BRAVE-AA1 study after 36 weeks of treatment with 4 mg baricitinib, 2 mg baricitinib or a **placebo**. More **efficacy** results can be found in **Document B**, **Section B.2.6**.

Figure 1. Key efficacy results for BRAVE-AA1 and BRAVE-AA2 after 36 weeks[33]



3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

Quality of life impact of baricitinib treatment

During BRAVE-AA1 and BRAVE-AA1, patients were asked to answer questions about their **quality of life**, using various different questionnaires called EQ-5D, HADS and SF-36. The results from these questionnaires showed that:[33-35]

- Patients treated with baricitinib had improvements in their **quality of life** compared to patients who had **placebo** after 36 weeks of treatment (HADS, SF-36)
- Patients treated with baricitinib had reduced symptoms of anxiety compared to patients receiving **placebo** after 36 weeks (HADS-Anxiety).
- Patients treated with baricitinib had reduced symptoms of depression after 36 weeks compared to patients receiving **placebo** (HADS-Depression).

Challenges with measuring quality of life in patients with AA

Although there were improvements in **quality of life** and symptoms of anxiety and depression in patients treated with baricitinib during BRAVE-AA1 and BRAVE-AA2, it is likely that these improvements were underestimated. This is because some of the questionnaires used to measure **quality of life** were not specific or relevant to AA. This means that the questionnaires may not have fully captured the positive impact of the hair regrowth from baricitinib on **quality of life**. The **quality of life** of patients at the start of the trial was also very high in some of the questionnaires, so there was not much room for improvement during the trial, even if they had significant hair regrowth.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Every medicine has its own **side effects** and the same medicine can produce different reactions in different people. In BRAVE-AA1 and BRAVE-AA2, baricitinib was generally well **tolerated**. No new **side effects** were discovered for baricitinib compared to the known **side effects** for baricitinib when it is used to treat other conditions.[33]

The most common **side effects** experienced by patients receiving baricitinib was **nasopharyngitis** (common cold) in BRAVE-AA1 and headaches in BRAVE-AA2. The most common **side effects**, which affected more or equal to 5% of patients in any group in BRAVE-AA1 and BRAVE-AA2, are summarised in **Table 3** below:[33]

Table 3. Summary of the most common side effects experienced by patients during BRAVE-AA1 and BRAVE-AA2[33]

Side effect	Percentage of patients with this side effect in BRAVE-AA1			Percentage of patients with this side effect in BRAVE-AA2		
	Placebo	2 mg baricitinib	4 mg baricitinib	Placebo	2 mg baricitinib	4 mg baricitinib
Upper respiratory tract infection	5.3%	4.9%	7.5%	7.1%	7.7%	6.4%
Headache	4.8%	4.4%	5.0%	6.5%	7.7%	9.0%
Nasopharyngitis	6.3%	6.6%	7.5%	4.5%	1.3%	6.4%
Acne	0.5%	5.5%	5.7%	1.9%	5.8%	4.7%
Urinary tract infection	1.6%	1.1%	2.5%	1.3%	7.7%	4.7%
Blood creatine kinase increased	1.6%	1.6%	5.7%	1.3%	0%	3.0%

Note: further explanation of the terms in orange are provided in the glossary (Section 4b).

The proportion of patients who experienced a more serious side effect or stopped their treatment (or "discontinued") because of side effects during BRAVE-AA1 and BRAVE-AA2 is shown in Table 4. There was a higher number of more serious side effects in patients who were treated with baricitinib compared with those receiving placebo. In BRAVE-AA1, there was also a higher number of people who received baricitinib who discontinued their treatment, especially in patients receiving 4 mg baricitinib. However, none of the differences were considered to have important implications for the medicine being used by patients in clinical practice. There were no deaths in either BRAVE-AA1 or BRAVE-AA2.[33]

Table 4. Summary of serious side effects and treatment discontinuations during BRAVE-AA1 and BRAVE-AA2.[33]

	Percentage of patients with this side effect in BRAVE-AA1			Percentage of patients with this side effect in BRAVE-AA2		
	Placebo	2 mg baricitinib	4 mg baricitinib	Placebo	2 mg baricitinib	4 mg baricitinib

Serious side effect	1.6%	2.2%	2.1%	1.9%	2.6%	3.4%
Side effect leading to discontinuation	1.1%	1.6%	1.8%	2.6%	2.6%	2.6%

Managing side effects

If a patient experiences any **side effects** while they are taking baricitinib, they should talk to their doctor, pharmacist or nurse as soon as possible. **Side effects** for baricitinib are usually manageable, but may require baricitinib treatment to be stopped temporarily until the **side effect** resolves, either on its own or after treatment.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

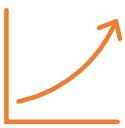
- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

The key benefits of baricitinib to patients include that:[6,33]

Baricitinib is one of the only treatment options for AA which has strong evidence showing that it is an effective treatment option in patients with severe AA

Baricitinib results in significant improvement in scalp hair regrowth for some patients and can also lead to almost complete recovery for a proportion of patients with severe AA

Some patients receiving baricitinib experience significant regrowth of the eyelashes and eyebrows within 36 weeks



The hair regrowth that occurs continues for at least 36 weeks after treatment is started in patients who respond to baricitinib treatment

The hair regrowth from baricitinib treatment leads to improvements in **quality of life** and reduces symptoms of anxiety and depression

Baricitinib can be taken by patients as a tablet, which is more convenient and is not uncomfortable or painful for patients, unlike some other management options for AA

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Baricitinib is generally well-tolerated and effective in leading to hair regrowth in some patients, however, some things that patients may want to consider before starting treatment include:

Efficacy

Baricitinib does not work for everyone and some patients might not experience any hair growth, despite taking baricitinib. Patients for whom baricitinib treatment does not work may still experience side effects, which are detailed further below.

Side effects

Like all medicines, some patients may experience **side effects** while they are taking baricitinib. As baricitinib interacts with the immune system, it may cause infections such as shingles and pneumonia, which may affect up to 1 in 10 people.[32] In the BRAVE-AA1 and BRAVE-AA2 trials, the most common **side effects** of baricitinib include **upper respiratory tract infections** (infection of sinuses and/or throat), headaches and **nasopharyngitis** (inflammation of nose and/or throat). These are usually manageable, and most patients do not need to stop treatment because of **side effects**.[33]

Administration

Baricitinib must be taken every day for as long as their AA continues. Patients may receive a reduced dose of baricitinib if the treatment is effective, but this still has to be taken every day. However, baricitinib can be taken as a tablet, which may be more convenient for patients, unlike some other AA treatments which must be given in hospital

by a doctor. Baricitinib does not have any important disadvantages compared with other treatment options that are currently available for patients with AA

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Healthcare administrators need to get the best value from their limited budgets. To do this, they want to know whether a new medicine provides 'good value for money' compared to existing medicines. They will look at the costs of the new medicine and how the health of patients is likely to improve if they take it. The pharmaceutical company that develops the medicines provides this information to healthcare administrators using a **health economic model**. The pharmaceutical company uses the **health economic model** to perform an analysis, which compares the costs and benefits of the new treatment (baricitinib) with the standard of care ("watch and wait").

How the model reflects AA

The economic model was designed to reflect the key features of AA and **clinical practice** in the UK. To do this, a model structure called a **Markov model** was chosen, as this type of model has been used previously for other similar skin conditions and so was considered the most relevant type of model for AA. The Markov model was used to model the experience of having AA over time and compares treatment with baricitinib versus watch and wait.

Modelling how much baricitinib improves hair regrowth

The results of the BRAVE-AA1 and BRAVE-AA2 trials were used to inform the economic model. The main result from the trials that was used in the model was **$SALT_{50}$**. **$SALT_{50}$** is defined as the proportion of patients who had at least 50% improvement in their hair growth (**SALT** score) compared to before treatment. This was the main result used in the

model because it was considered relevant to what would be considered a successful outcome when treating AA in **clinical practice**.

The results of the BRAVE-AA1 and BRAVE-AA2 trials cover a total of 36 weeks, however the economic model simulates patients for the rest of their lifetime, a much longer period of time than the length of the trial. Most patients will stop treatment for AA at some point, meaning that the model has to estimate the number of patients discontinuing their treatment for any time that is longer than the 36 weeks of the trial. In the model, this rate of discontinuation was estimated to be the same as the rate of patients discontinuing treatment during the trial.

Modelling how much baricitinib improves quality of life

An improvement in **quality of life** was modelled when a patient experiences more than a 50% improvement in their hair growth. This reflects the fact that the mental and emotional impact of AA would likely be reduced when a patient experiences hair regrowth.

The **quality-of-life** data that informed the model were from a **real-world evidence** study of patients with AA. In this study, **quality of life** was measured using a questionnaire called EQ-5D, as this was the best source of robust data (see **Section 3f** for more information on this).

Modelling how the costs of treatment differ with the new treatment

Various different costs are included in the model for the different AA treatments. These costs include:

- The cost of the medicine itself and how much it costs to administer the medicine
- The cost of starting treatment and the cost of monitoring the patients during treatment

Baricitinib is expected to reduce some costs for the NHS compared to watch and wait for patients with severe AA. The key reasons for this include that:

- Baricitinib leads to reduced costs associated with treating anxiety and depression or other psychological illnesses caused by AA. This is because baricitinib causes a reduction in anxiety and depression in patients compared to watch and wait.
- Current treatment options for AA are associated with higher monitoring and disease management costs than baricitinib. For instance, patients treated with baricitinib have fewer appointments with doctors and/or nurses than patients undergoing watch and wait.

Uncertainty

There are various assumptions that were made in the model. Information on these assumptions can be found in **Document B**, **Section 3.6.2**.

A key assumption in the model was the definition of ‘response’, used to indicate whether a patient had clinically meaningful hair regrowth and therefore whether they should be modelled to continue treatment with baricitinib/watch and wait or have another type of treatment instead. In the model, patients achieving **$SALT_{50}$** (the proportion of patients achieving at least a 50% improvement in hair growth) were considered to have a

response. However, a variation of this assumption was also tested in the model. In this variation, patients achieving **SALT$_{75}$** (the proportion of patients achieving at least a 75% improvement in hair growth) were considered to have responded to treatment instead.

Variations of other inputs in the model were also tested and the results of these tests are explained in **Document B, Section B.3.8.3**.

Cost effectiveness results

Overall, the results of the cost effectiveness analysis show that treatment was associated with higher costs, but also higher benefits (or '**quality-adjusted life years**' [**QALYs**]) than watch and wait. This resulted in an **incremental cost-effectiveness ratio** (**ICER**) of £29,111 per QALY gained.

Benefits of baricitinib not captured in the economic analysis

Compared to some other treatments used in AA, baricitinib also does not require any uncomfortable procedures (such as topical immunotherapy) as it is given as a tablet. This may improve patient experience by reducing any discomfort associated with AA treatment and by being a more convenient option for patients.

Conclusion

The benefits outlined in **Section 3h** and the economic analysis results above suggest that baricitinib is an effective new treatment for patients with severe AA but is more costly to the NHS than a 'watch and wait' strategy.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations.

If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)

Baricitinib is an innovative treatment which would represent an important advancement in the treatment of AA

AA is a condition that can have a significant effect on a patient's mental and emotional wellbeing and **quality of life**. Despite this, there are very few treatment options available that have been shown to be effective in patients with severe AA. Many of these treatment options also cause uncomfortable or unpleasant **side effects**.[6]

Baricitinib is an innovative medicine that **treats the underlying cause of AA**. It is the **first treatment for AA that has strong evidence** that shows it is effective in patients with severe AA. Baricitinib would therefore give patients the **opportunity to experience improved hair regrowth** compared to current treatment options, **reducing the negative impact that AA has on a patients' life**.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged.

Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics

More information on how NICE deals with equalities issues can be found in the NICE equality scheme

Find more general information about the Equality Act and equalities issues here

There are no equality issues that are anticipated for the use of baricitinib in adults with severe AA.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc.
Where possible, please provide open access materials or provide copies that patients can access.

Further information on AA:

- British Association of Dermatologists' guidelines for the management of alopecia areata 2012 British Association of Dermatologists' guidelines for the management of AA
- Alopecia UK Alopecia UK website

Further information on NICE and the role of patients:

- Public Involvement at NICE Public involvement | NICE and the public | NICE Communities | About | NICE
- NICE's guides and templates for patient involvement in HTAs Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE
- EUPATI guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/
- EFPIA – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- INAHTA: http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

This glossary explains terms highlighted in **orange** in this document. At times, an explanation for a term might mean you need to read other terms to understand the original terms.

Alopecia totalis	A type of AA where there is complete loss of hair on the scalp.
Alopecia universalis	A type of AA where there is complete loss of all body hair, including the scalp.
Autoimmune disease	A condition in which your **immune system** mistakenly attacks your body. There are lots of different types of autoimmune diseases, where the immune system attacks different parts of the body.

Blood creatine kinase	Creatine kinases is a type of **protein** that is normally found in the blood. However, if the levels of this protein are increased, it indicates that there may be damage or disease of the muscles, heart or brain.
Cataracts	A condition where the lens, a small transparent disc inside your eye, develops cloudy patches.
Clinical trial/clinical study	A type of research study that tests how well new medical approaches work in people. These studies test new methods of screening, prevention, diagnosis or treatment of a disease. Also called a clinical study.
Diabetes	A serious condition where your blood glucose level is too high. It can cause symptoms like excessive thirst, needing to urinate a lot and tiredness. It can also increase your risk of getting serious problems with your eyes, heart and nerves.
Efficacy	The ability of a drug to produce the desired beneficial effect on your disease or illness in a **clinical trial.**
Folliculitis	A skin condition where **hair follicles** become inflamed. It may look like small red bumps or white-headed pimples around **hair follicles**.
Hair follicle	A small pocket or opening in the skin through which the hair grows.
Health economic model	A way to predict the costs and effects of a technology over time or in patient groups not covered in a **clinical trial**.

Histopathology	The study of organs, tissues, cells and genetics, which involves examining tissues and/or cells under a microscope.
Hypopigmentation	Patches of skin that are lighter than someone's overall skin tone
Incremental cost-effectiveness ratio	The incremental cost-effectiveness ratio (ICER), is the difference in the change in mean costs in the population of interest divided by the difference in the change in mean outcomes in the population of interest.
Immune system	A complex network of cells, tissues, organs and the substances they make that helps the body fight infections and other diseases.
Immunosuppressant	Medicines that prevent activity of the **immune system**.
Intralesional steroids	The direct injection of a **steroid** into the skin.
Janus kinase	A type of **protein** found inside the cell which plays a role in inflammation.
Janus kinase inhibitors	A type of drug which blocks the activity of **Janus kinase proteins.**
Marketing authorisation	The legal approval by a **regulatory body** that allows a medicine to be given to patients in a particular country.
Markov model	A type of **health economic model**.

Medicines and Healthcare products Regulatory Agency (MRHA)	The **regulatory body** that evaluates, approves and supervises medicines throughout the European Union.
Nasopharyngitis	Inflammation of the throat (pharynx) and nose.
Non-scarring	Does not cause scarring.
Off-label	When a drug is used for a disease or medical condition that it is not approved to treat.
Osteoporosis	A health condition that weakens bones, making them fragile and more likely to break.
Patchy AA	A type of AA where there is one or multiple patches of hair loss on the scalp.
Phase 3 clinical trial	This type of **clinical trial** that tests the safety and how well a new treatment works compared with a standard treatment. For example, it evaluates which group of patients has better survival rates or fewer **side effects**.
Placebo	A treatment that appears real, but has no therapeutic benefit. It is used in clinical trials to compare treatments to.
Protein	These are structures inside all cells of our body that are important for many activities including growth and repair.
Psychological support	Support given to help meet the mental, emotional, social, and spiritual needs of patients and sometimes their family. This is often in the form of counselling, where

	patients talk about their emotional and mental health.
Quality-adjusted life year	A measure of the state of health of a person, where the length of life is adjusted to reflect the quality of life. One quality-adjusted life year (QALY) is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale). It is often measured in terms of the person's ability to carry out the activities of daily life, and freedom from pain and mental disturbance.
Quality of life	The overall enjoyment of life. Many **clinical trials** assess the effects of cancer and its treatment on the quality of life of patients. These studies measure aspects of a patient's sense of well-being and their ability to carry out activities of daily living.
Real-world evidence	Evidence that has come from routine clinical practice and not a **clinical trial**.
Regulatory bodies	These are legal bodies that review the quality, safety and **efficacy** of medicines and medical technologies.
Severity of Alopecia Tool, or SALT	A special measurement that can be used to assess how much (or the 'extent') of hair loss a patient has. The SALT is used to calculate a patient's **SALT score.**
SALT score	The **SALT** is used to calculate a patient's SALT score, which ranges from 0–100. A SALT score of 100 indicates complete scalp hair loss and a score of 0 indicates no hair loss.

Side effect (also called adverse event)	An unexpected medical problem that arises during treatment. Side effects may be mild, moderate or severe.
Steroids	A type of medicine which reduce inflammation.
Stomach ulcers	Sores that develop on the lining of the stomach. The most common symptom of a stomach ulcer is a burning or gnawing pain that develops in the stomach.
Tolerated	The ability of a patient to put up with the **side effects** of treatment.
Topical	A medicine that is applied to the skin.
Trichoscopy	A specialist device that can take magnified images of the scalp and **hair follicle**. This allows the doctor to determine scalp and hair root health.
Ultraviolet light treatment (PUVA)	A treatment which involves taking a drug called PSORALEN (P) and then exposing the skin to ultraviolet light.
Upper respiratory tract infection	An infection that affects the sinuses and throat.
Urinary tract infection	An infection of your bladder, kidneys or the tubes connected to them.

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