MARKET ACCESS CHALLENGES FOR NOVEL THERAPIES FOR TREATMENT OF SEVERE ALOPECIA AREATA

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HTA333

BACKGROUND

- Alopecia areata (AA) is an immune-mediated disease that causes non-scarring hair loss from the scalp and other areas of the body.[1]
- Apart from visible physical impact, AA influences psychosocial health, leading to emotional distress and decreased quality of life (QoL).[2]
- The approval of Janus kinase inhibitors (JAKi), including baricitinib and ritlecitinib for severe AA, defined as ≥50% scalp hair loss, was a breakthrough in the treatment, which previously was limited to not-licensed drugs and non-pharmacological management (e.g., wigs).[3-7]

OBJECTIVE

- The aim of this study was to explore how identical clinical trial evidence led to differing reimbursement decisions in four European countries (France, Germany, Sweden, and the UK).

METHODS

- The design and results of two pivotal trials for JAKi were analysed.
- Then, a review of Health Technology Assessment (HTA) reports and reimbursement decisions in France (HAS), Germany (G-BA), Sweden (TLV), and the UK (NICE) for identified JAKi was conducted.

RESULTS

- Regulatory details of JAKi approved in severe AA are presented in Figure 1.[4-7]
- Both JAKi were studied in well-designed randomised placebo-controlled trials in adults (and adolescents for ritlecitinib), with severe AA affecting more than 50% of the scalp surface area. They showed high efficacy in hair regrowth (≤20% and ≤10% scalp hair loss) as a primary endpoint, with lash and eyebrow regrowth as secondary endpoints; however, meaningful improvement in QoL was not demonstrated. The safety profile of both drugs was favourable compared to placebo (Table 1).[8-12]
- As no standard of care in severe AA is clearly defined, placebo was considered acceptable by all HTA agencies. However, the countries had varied views on the disease (severe vs. cosmetic), the intervention (lifestyle drug or not), and the outcomes (no QoL improvement), leading to different reimbursement decisions (Figure 2).[13-19]

Table 1. Summary of pivotal clinical trials for JAKi in the treatment of severe AA[8-12]

		BARICITINIB		RITLECITINIB
		BRAVE-AA1 (N = 654)	BRAVE-AA2 (N = 546)	ALLEGRO (N = 718)
Study design		Randomized, double-blind, placebo-controlled, phase III		Randomized, double-blind, placebo-controlled, phase IIb/III
Population		• Adults with severe AA (≥50% scalp hair loss), • Current episode of AA lasting >6 months to <8 years, without spontaneous improvement during the previous 6 months		• Adults and adolescents (12-17 years) with severe AA (≥50% scalp hair loss), • Current episode of AA lasting >6 months to <8 years, without spontaneous improvement during the previous 6 months
Intervention		**Baricitinib (BAR)**, oral once-daily		**Ritlecitinib (RIT)**, oral once-daily
Comparator		**Placebo (PLC)**, patients were prohibited from using other treatments for AA		**Placebo (PLC)**, patients were prohibited from using other treatments for AA
Duration		36 weeks (double-blind) + 68 weeks (long-term extension) + 96 weeks (bridging extension)		24 weeks (double-blind) + 24 weeks (extension)
Endpoints		*Primary:* • **The proportion of patients achieving SALT score ≤20 (≤20% scalp hair loss) at week 36** *Other:* • Many secondary efficacy endpoints related to hair, eyebrow, or eyelash loss; • QoL (generic scales: EQ-5D-5L, SF-36, disease-specific scales: Skindex-16 adapted for AA; other: HADS); • Safety		*Primary:* • **The proportion of patients achieving SALT score ≤20 (≤20% scalp hair loss) at week 24** • **The proportion of patients achieving SALT score ≤10 (≤10% scalp hair loss) at week 24** - *primary endpoint for EMA* *Other:* • Many secondary efficacy endpoints related to hair, eyebrow, or eyelash loss; • QoL (generic scales: EQ-5D-5L, EQ-5D-Y, VAS, SF-36, HADS; disease-specific scales: AAPPO, WPAI: AA); • Safety
Efficacy results[a]	SALT score ≤20	✓ BAR 2 mg vs. PLC: **22.8%** vs. **6.2%** (p<0.001) ✓ BAR 4 mg vs. PLC: **38.8% vs. 6.2%** (p<0.001)	✓ BAR 2 mg vs. PLC: **19.4%** vs. **3.3%** (p<0.001) ✓ BAR 4 mg vs. PLC: **35.9% vs. 3.3%** (p<0.001)	✓ RIT 50 mg vs. PLC: **23% vs. 2%** (p<0.0001)
	SALT score ≤10	✓ BAR 2 mg vs. PLC: **13.0% vs. 4.1%** (p=0.002) ✓ BAR 4 mg vs. PLC: **27.9% vs. 4.1%** (p<0.001)	✓ BAR 2 mg vs. PLC: **12.0%** vs. **1.0%** (p=0.002) ✓ BAR 4 mg vs. PLC: **25.6% vs. 1.0%** (p<0.001)	✓ RIT 50 mg vs. PLC: **14%** vs. **2%** (p=0.0002)
	Other	✓ Generally **favoured BAR** over PLC (at a dose of 4 mg but not at a dose of 2 mg)		✓ Generally **favoured RIT** over PLC
QoL results[a]		× Meaningful improvement **was not shown**		× Meaningful improvement **was not shown**
Safety results[a]		✓ Acceptable profile **was shown**		✓ Acceptable profile **was shown**

a. Only results for approved posology were presented.

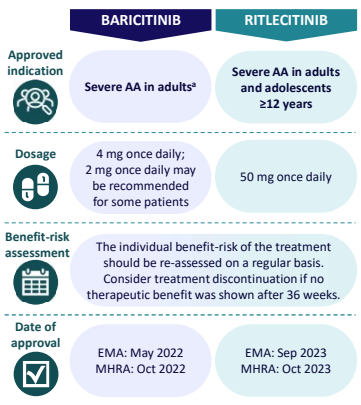
France

- Both JAKi were recommended by HAS due to the high unmet need in this severe disease and efficacy demonstrated on relevant primary endpoints, with SMR important and moderate for baricitinib and ritlecitinib, respectively. The lack of proven additional benefit in QoL and safety issues, previously observed for JAKi in other indications, resulted in minor added benefit (ASMR IV).[13,14]

UK

- Baricitinib was not recommended by NICE despite acknowledging the severity of AA and the improvement in hair regrowth compared with placebo. The negative decision was driven by the lack of a documented impact on QoL in the disease with a profound psychological burden and a need for long-term or indefinite treatment to avoid recurrence of hair loss, which puts patients at risk of serious side effects, that all together with the requested price resulted in an unacceptable cost-effectiveness level.[15]

Figure 1. Summary of approved indication of JAKi in severe AA[4-7]



a. Baricitinib is also indicated for the treatment of rheumatoid arthritis, atopic dermatitis, and juvenile idiopathic arthritis.

- In contrast to baricitinib, ritlecitinib was recommended by NICE. To address small changes in disease-specific QoL measurement from the clinical study, attributed to characteristics of the study population and the inability of generic instruments (recommended by NICE to generate utility values) to capture the effects of AA on daily living, the company estimated utility from an additional vignette study. This allowed to better capture QoL impact. The use of a conservative estimate for time on treatment decreased uncertainty, and a lower drug price reduced the cost. All of these made cost-effectiveness achievable.[16]

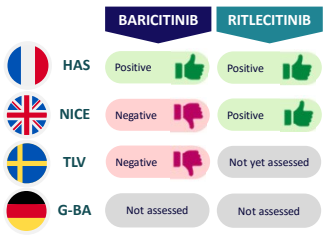
Sweden

- Similarly to the NICE assessment, baricitinib was not recommended by TLV due to uncertainties in QoL benefit, safety concerns, and unacceptable cost-effectiveness.[17] Ritlecitinib was not yet assessed.

Germany

- In Germany, both drugs are seen as lifestyle drugs and AA as a "cosmetic problem" that can be resolved with wearing a wig. Lifestyle drugs are not considered by G-BA for reimbursement.[18,19]

Figure 2. Summary of HTA agencies' decisions on JAKi in the treatment of severe AA[4-7,13-19]



CONCLUSIONS

- **Reimbursement decisions for JAKi in severe AA varied in analysed countries despite similar results from pivotal studies.**
- **The differences between countries were driven by various perceptions of the disease and the consideration of QoL data. Unlike in France, the UK and Sweden, in Germany AA is considered a cosmetic condition treated by lifestyle drugs. The lack of impact on QoL resulted in minor added benefit in France (ASMR IV), with unacceptable cost-effectiveness due to high price in the UK and Sweden leading to a negative recommendation for baricitinib.**
- **Different reimbursement decisions between the two drugs assessed by the same HTA agency resulted from diverse approaches to data assessment in terms of QoL (e.g., using utilities from clinical trials vs. utilities from vignette studies) and price strategy.**
- **Although previously placebo was considered an appropriate comparator, future JAKi must consider an active comparator (baricitinib, ritlecitinib) as an additional hurdle.**

ABBREVIATIONS

AA – alopecia areata; **AAPPO** – Alopecia Areata Patient Priority Outcomes; **BAR** – baricitinib; **EQ-5D-Y** – EQ-5D Youth; **G-BA** – Gemeinsame Bundesausschuss; **HADS** – Hospital Anxiety and Depression Scale; **HAS** – Haute Autorité de Santé; **HTA** – health technology assessment; **JAKi** – Janus kinase inhibitor; **NICE** – National Institute for Health and Care Excellence; **QoL** – quality of life; **RIT** – ritlecitinib; **SALT** – Severity of Alopecia Tool; **SF-36** – short form-36; **TLV** – Tandvårds-Läkemedelsförmånsverket; **VAS** – Visual Analogue Scale; **WPAI: AA** – Work Productivity and Activity Impairment: Alopecia Areata

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12. EMA, Ritlecitinib EPAR
13. HAS, Baricitinib for severe AA
14. HAS, Ritlecitinib for severe AA
15. NICE, Baricitinib for severe AA
16. NICE, Ritlecitinib for severe AA
17. TLV, Baricitinib for severe AA
18. G-BA, Baricitinib for severe AA
19. G-BA, Ritlecitinib for severe AA