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Efficacy and safety of Cinainu in paediatric alopecia areata: an international, double-blind, randomized, placebo-controlled, phase II/III trial

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Abstract

Background Alopecia areata (AA) is a debilitating autoimmune-mediated disorder marked by nonscarring hair loss. It significantly impairs patients' quality of life (QoL). Inflammation and immune dysregulation, especially involving chemokines like interleukin-8 and Janus kinase (JAK)-dependent signalling pathways, underlie AA pathogenesis. As oral JAK inhibitors are approved for severe cases only, unmet needs persist, particularly for paediatric patients and those with moderate AA. Cinainu, a topical solution containing four botanical extracts, may address these gaps due to its anti-inflammatory, anti-apoptotic and antioxidant properties.

Objectives This phase II/III study evaluated the efficacy and safety of Cinainu in children and adolescents with moderate-to-severe AA.

Methods The RAAINBOW study, an international, double-blind, placebo-controlled trial, involved 107 paediatric patients randomly assigned (2 : 1) to receive Cinainu or placebo for 24 weeks, followed by a 24-week untreated follow-up period. The primary analysis included 62 patients meeting predefined criteria for moderate-to-severe AA. The primary endpoint was the relative change in Severity of Alopecia Tool (SALT) score from baseline to Week 24. Secondary outcomes included responder rate (≥ 40% improvement in SALT score from baseline to Week 24), absolute SALT score changes, and QoL improvements measured by the Children's Dermatology Life Quality Index (CDLQI) and EuroQol Visual Analogue Scale (EQ-VAS). Safety assessments included treatment-emergent adverse events. This trial is registered with EudraCT: 2016-003208-30 and ClinicalTrials.gov: NCT03240627.

Results Cinainu showed significant benefits compared with placebo in relative change in SALT score from baseline to Week 24: adjusted mean difference [95% confidence interval CI)] + 26.3% (0.1–52.5); $P = 0.0488$, Cohen's d = 0.52. A significantly higher proportion of Cinainu-treated patients met responder criteria at Week 24 (26.2% vs. 5.0%; $P = 0.0484$). Cinainu also led to significant QoL improvements at Week 24, with effect sizes of d = 0.61 in CDLQI and d = 0.69 in EQ-VAS. Benefits were sustained during the follow-up period: adjusted mean difference (95% CI) + 39.4% (13.1–65.6); $P = 0.0033$, Cohen's d = 0.80, in relative change in SALT score from baseline to Week 48 and large effect sizes in CDLQI (d = 0.79). No serious adverse events were related to Cinainu, and treatment was well tolerated.

Conclusions In this study, Cinainu showed efficacy, safety and sustained benefits during follow-up in children and adolescents with moderate-to-severe AA, a population with significant unmet needs.

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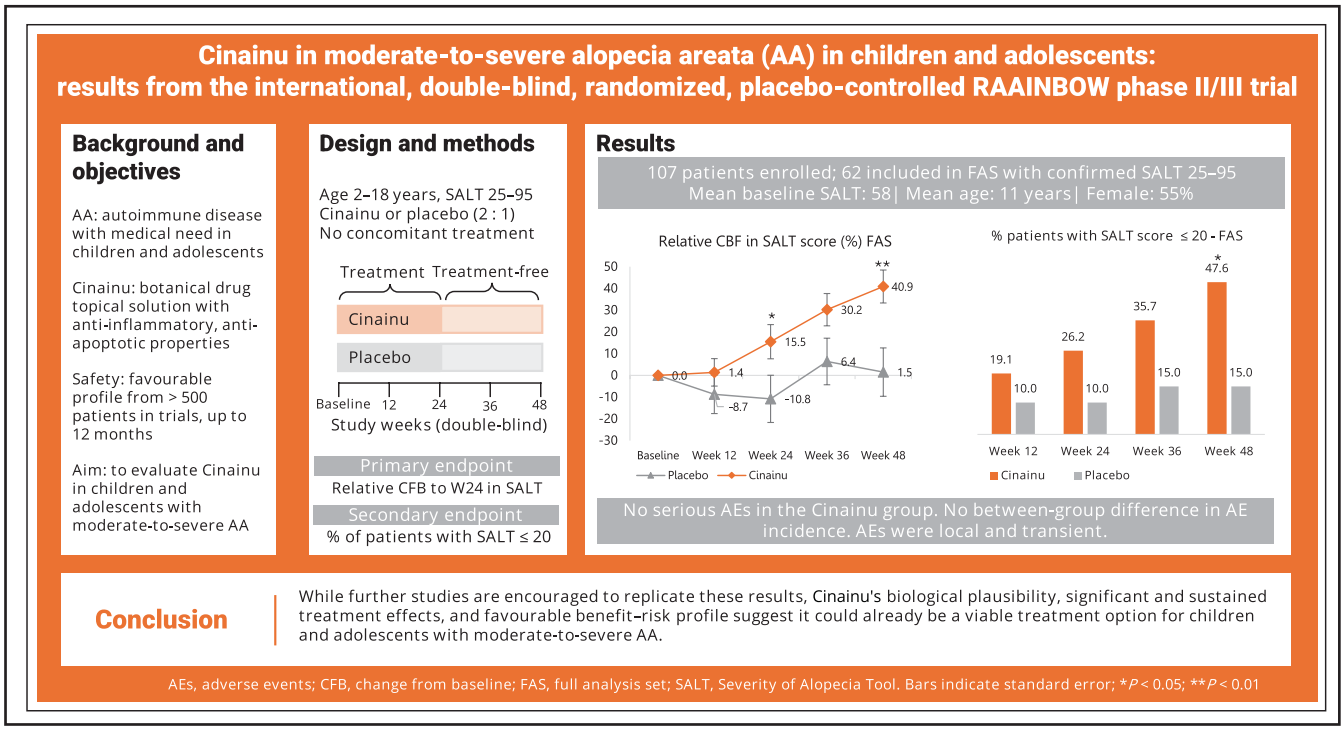
Graphical Abstract



Lay summary

Alopecia areata (AA) is an autoimmune condition. The body's immune system attacks hair follicles, causing patchy to total scalp or body hair loss. AA affects about 2 in 100 people worldwide and often starts in childhood or adolescence. AA can be very distressing for people, especially younger people. The condition can impact self-esteem and quality of life. Currently, there is no approved treatment for moderate AA in children. No topical treatment (i.e. applied directly to a body location, such as the scalp) is approved for any form of AA in any age group.

This study looked at children and adolescents with moderate-to-severe AA in Bulgaria, France, Germany and India. We tested the safety and effectiveness of a new botanical (i.e. from plants) drug-based topical solution called Cinainu. The study included 107 patients with AA aged 2 to 17 years. Participants were randomly assigned to apply either Cinainu or a placebo solution to their scalp twice daily for 24 weeks. After the treatment ended, participants were followed for another 24 weeks to see whether any benefits lasted. Cinainu led to better hair regrowth compared with the placebo. By Week 24, children with AA using Cinainu had 26% more hair regrowth on average than those using the placebo. More than one in four children using Cinainu had noticeable improvement. This was compared with just one in 20 in the placebo group. Cinainu-treated participants also reported greater improvements in appearance and wellbeing compared with those receiving placebo. These benefits persisted even after treatment ended. Cinainu was well tolerated, with only mild and temporary side effects reported.

These results suggest that Cinainu could offer a safe and effective new treatment option for children with moderate-to-severe AA. This will help to fill an important gap in current care.

What is already known about this topic?

- There are no approved topical treatments for alopecia areata (AA), and current approved therapies are limited to adults and adolescents with severe disease.
- Cinainu cutaneous solution is an investigational medicinal product composed of *Allium cepa, Citrus limon, Paullinia cupana* and *Theobroma cacao*.
- Cinainu has previously shown efficacy in the treatment of androgenetic alopecia and persistent chemotherapy-induced alopecia in adults.

What does this study add?

- This international, double-blind, placebo-controlled trial evaluated Cinainu in 107 children and adolescents (2–17 years of age) with moderate-to-severe AA, including a 24-week treatment phase and 24-week follow-up.
- In the primary analysis population ($n=62$), Cinainu was superior to placebo in improving hair growth and quality of life at the end of both the treatment period and the follow-up period.
- Cinainu was well tolerated with a safety profile similar to placebo.

Alopecia areata (AA) is an autoimmune-mediated disease that causes nonscaring, patchy to total hair loss on the scalp or body.[1] AA lifetime incidence is approximately 2%,[1] with 19–36% of cases affecting children and adolescents.[2] Early-onset AA is associated with a poorer prognosis.[3,4] AA significantly impairs quality of life (QoL),[5] particularly among young males, with links to depression, anxiety and bullying.[6–9]

AA pathogenesis involves immune dysregulation driven by cytokines including interferon (IFN)-γ, interleukin (IL)-15 and IL-8/CXCL8.[10–14] These signals – particularly IL-8, which recruits immune cells to the follicle[15,16] – contribute to immune privilege collapse and hair matrix cell apoptosis.[12–14] Signalling by IFN-γ and IL-15 requires Janus kinase (JAK) proteins.[10,11,17]

While three oral JAK inhibitors are now approved for severe AA in adults and one in adolescents,[18–20] unmet needs remain – particularly for moderate disease and paediatric populations. Most AA cases are of mild or moderate severity,[4] and JAK inhibitors are not indicated in these groups. Additionally, relapse occurs in 80% of patients after treatment discontinuation, implying a need for sustained immunosuppression.[21] No topical treatments are currently approved for AA, despite patient preferences for topical options with minimal systemic exposure.[22]

Cinainu – previously known as coacillium or LH-8 – is a drug candidate composed of extracts from four plants – *Allium cepa*, *Citrus limon*, *Paullinia cupana* and *Theobroma cacao* – all designated as generally recognized as safe (GRAS) or the equivalent by the US Food and Drug Administration. It is formulated as a scent-free, nonoily, nonsticky, fast-absorbing topical solution. Selected for their anti-immunoinflammatory, antioxidant,[23,24] anti-apoptotic[25] and antimicrobial properties,[26] these plants target various alopecia mechanisms.

In preclinical studies, Cinainu reduced endothelial expression of T-cell chemotaxin IL-8 and pro-inflammatory adhesion molecules (E-selectin, ICAM-1) (File S1; see Supporting Information), restored perifollicular anti-apoptotic protein Bcl-2 to near-normal levels, increased the density of epidermal Langerhans cells, and increased scalp collagen content.[25,27] In clinical studies, Cinainu showed a favourable safety profile and positive effects on hair growth in patients with androgenetic alopecia and persistent chemotherapy-induced alopecia.[28,29] Collectively, these results suggest that Cinainu could address unmet medical needs in AA.

Here, we report the results from the RAAINBOW study, a phase II/III trial testing the efficacy and safety of Cinainu in children and adolescents with moderate-to-severe AA.

Materials and methods

Study design and participants

RAAINBOW was a double-blind, randomized, parallel-group, placebo-controlled trial conducted at 12 sites across Bulgaria, France, Germany and India. The protocol followed the Uniform Protocol for Alopecia Areata Clinical Trials, a template harmonizing key features of phase II/III AA trials,[30] and was accepted by the Paediatric Committee of the European Medicines Agency (File S2; see Supporting Information). The trial included a 4-week screening phase, a 24-week treatment phase, and a 24-week treatment-free follow-up.

Patient eligibility was assessed during the screening visit using the Severity of Alopecia Tool (SALT)[31] to quantify the percentage of scalp hair loss, without adjustment for paediatric vs. adult head size, as these differences were deemed not clinically relevant. Inclusion criteria were (i) age ≥ 2 years and < 18 years; (ii) moderate (SALT score 25 to < 50) or severe (50 to < 95) scalp AA at screening; (iii) current AA episode duration between 6 months and 3 years. Concomitant treatment for hair growth was prohibited during the study period. Full inclusion/exclusion criteria and methodological justifications are available in Files S3 and S4 (see Supporting Information). This trial is registered with EudraCT: 2016-003208-30 and ClinicalTrials.gov: NCT03240627.

Randomization and blinding

Patients were randomly assigned in a 2 : 1 ratio to receive either Cinainu or placebo, allowing greater exposure to Cinainu to better characterize its safety profile. Randomization was performed using a block size of six patients and was stratified by study site. The placebo was identical to the Cinainu cutaneous solution in appearance and smell. The sponsor, clinical research organizations, investigators, study-site personnel and patients were blinded to treatment assignments, and blinding integrity was maintained throughout the study until the database lock.

Procedures

Patients or their parents applied Cinainu or placebo to the entire scalp twice daily for 24 weeks, using an age-adjusted dosing regimen selected based on prior adult studies showing efficacy with 1.01 mL per application.[28] To maintain a proportional scalp surface-to-dose ratio in younger children,

those aged 2–15 years received seven sprays (0.88 mL) and those over 15 years received eight sprays (1.01 mL) per application.

Patients were evaluated at each visit. These evaluations comprised a clinical examination, standardized photographic documentation, administration of the Children's Dermatology Life Quality Index (CDLQI)[32] and the EuroQol Visual Analogue Scale (EQ-VAS).[33] The CDLQI (range 0–30; lower scores indicate better QoL)[32] was administered to participants aged ≥ 4 years. The EQ-VAS (range 0–100; higher scores indicate better QoL)[33] was completed by children aged ≥ 8 years. The SALT score was independently assessed by trained investigators and an expert, both blind to treatment condition and each other's evaluations. Investigators used physical examination and standardized photographs, and the expert relied on the same photographs.

Endpoints

The primary efficacy endpoint was the relative change in SALT score from baseline to Week 24. Key secondary outcomes were the proportion of patients with a relative change in SALT score ≥ 40% from baseline to Week 24 ('Responder'), and the absolute change in SALT score from baseline to Week 24. Other secondary endpoints included the relative and the absolute change in SALT score from baseline to Week 48, the changes from baseline in CDLQI and EQ-VAS scores at each evaluation timepoint, and the number of new areas of alopecia between baseline and Week 24. Additionally, the percentage of patients who achieved a SALT score ≤ 20 or ≤ 10, and SALT score at each timepoint were analysed post hoc.

Treatment compliance was assessed by comparing the actual weight of returned solution bottles with the expected weight based on the age-dependent dosing regimen.

The main safety assessments included adverse events (AEs) and treatment-emergent AEs (TEAEs).

Statistical analysis

The sample size calculation was based on a minimal standardized effect size (Cohen's d) of 0.75, corresponding to a 24% group difference in SALT score change and a standard deviation of 32%. With significance level of $\alpha = 0.05$ (two-sided), 87 patients (58 Cinainu, 29 placebo) would provide 90% power. Accounting for a 14% post-randomization dropout rate, 102 patients were planned for randomization.

The full analysis set (FAS) was predefined in the Statistical Analysis Plan (SAP) as the primary population for all the efficacy analyses. The FAS included all randomized subjects who had a SALT score between 25 and 95 at randomization, as confirmed by both the investigators and the expert (raters). Literature evidence suggests that, in contrast to moderate-to-severe AA, spontaneous hair regrowth is common in patients with < 25% scalp hair loss (SALT < 25), occurring in 67–80% of cases.[34,35] In addition, spontaneous improvements between screening and randomization can occur, especially in patients with mild-severity AA, and can compromise the demonstration of efficacy.[36,37] To ensure assay sensitivity and in line with the primary objective of the trial, the FAS included only those with SALT score between 25 and 95 according to both raters at randomization, reflecting clear cases of moderate-to-severe scalp hair loss. Patients included in the study based on investigators' measurement at screening but determined by the expert or the investigator to have a SALT score outside the 25–95 range at randomization (i.e. 3–28 days after screening) were allocated to the intention-to-treat (ITT) population but excluded from the FAS. Additional data on the FAS and its validity as primary analysis population are presented in File S5 (see Supporting Information). Safety analyses were conducted in the ITT population which included all randomized patients. To explore the effect of Cinainu in a broader population, efficacy analyses were also conducted in the ITT population.

The relative change in SALT score from baseline to Week 24 was analysed using a mixed model for repeated measures (MMRM) with treatment, visit, treatment-by-visit interaction as fixed effects, and severity of AA at baseline as a covariate. An unstructured covariance matrix pattern was used to estimate the within-subject correlations over repeated measures. Before using the MMRM model, a pattern-mixture model with multiple imputation was applied for patients with no post-baseline SALT score ($n = 5$ in the FAS, including $n = 4$ in the Cinainu group).

A sensitivity analysis using the above MMRM model but with the rank-transformed response as the outcome was performed to evaluate the effect of potential outliers. To assess the risk of bias due to missing data, sensitivity analyses using control-based pattern multiple imputation, baseline observations carried forward, multiple imputation, last observation carried forward or observed cases methods were conducted. The potential influence of baseline variables (e.g. SALT score, age, disease duration) on treatment effect was assessed by including interaction terms in the MMRM model.

If the null hypothesis was rejected for the primary analysis of the primary endpoint, the confirmatory testing of the hypotheses for the key secondary endpoints was performed in a hierarchical manner. In case the null hypothesis was not rejected, the analysis of the key secondary efficacy endpoints was considered as exploratory only. Secondary endpoints on SALT score at each timepoint or change in SALT score were analysed using the same methods as for the primary analysis of the primary endpoint. CDLQI and EQ-VAS scores were analysed with a MMRM model. The differences in proportion of responders were tested using the Pearson χ^2 statistic. The statistical significance level was set at 5% for all hypothesis tests.

Inter-rater reliability for SALT score assessments was estimated at each timepoint using the intraclass correlation coefficient (ICC). As predefined in the SAP, the investigator-assessed SALT scores were used for baseline characteristics and efficacy analyses.

All AEs were coded according to the Medical Dictionary for Regulatory Activities version 25.1. The proportions of patients that reported AEs were tabulated by group.

The principal statistical software used was SAS®, version 9.4. PROC MIXED was used for performing MMRM models. Data from an earlier provisional analysis were presented at a conference. All efficacy data reported in this article are based on final analyses conducted in accordance with the protocol and the SAP, and subject to quality control procedures.

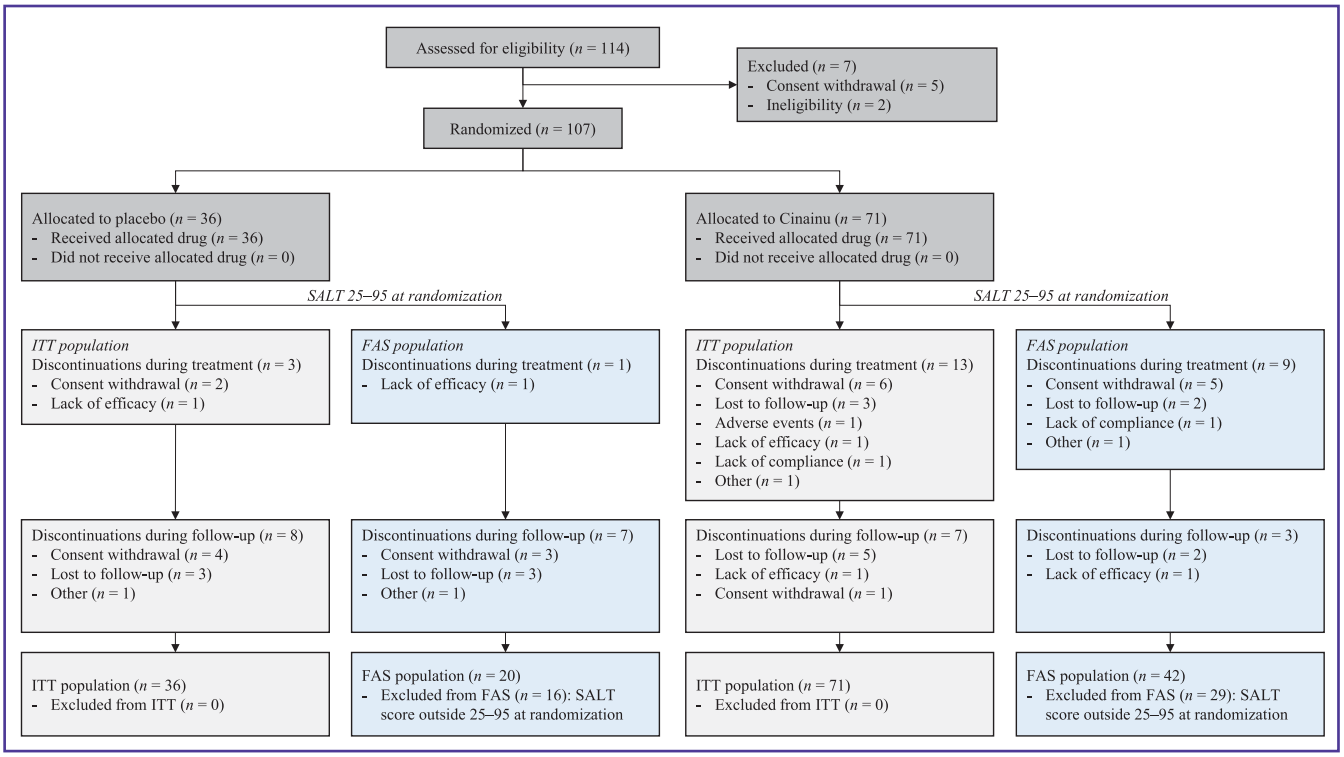


Figure 1 Flow diagram. FAS, full analysis set; ITT, intention-to-treat; SALT, Severity of Alopecia Tool.

Results

Patients

From February 2018 to September 2021, 114 patients were screened, and 107 were included in the ITT population and randomly assigned in either the Cinainu group ($N=71$) or the placebo group ($N=36$). A total of 76 (71%) patients completed the study (Cinainu, $n=51$, 72%; placebo, $n=25$, 69%) (Figure 1). Among these 107 randomized patients, 62 were included in the FAS (Cinainu, $n=42$; placebo, $n=20$). Of those, 52 (84%) and 42 (68%) patients completed the treatment and study periods, respectively (Figure 1).

High inter-rater reliability was observed between investigator and expert SALT assessments across all visits in both the ITT and FAS populations (ICC > 0.85; File S6; see Supporting Information). Of the 107 randomized patients, 62 were included in the FAS. Exclusions from the FAS were due either to changes in disease severity between screening and randomization (8 patients whose SALT scores shifted outside the 25–95% range) or to discrepancies between investigator and expert assessments of SALT score at randomization (37 patients), where one assessment was within the 25–95% range and the other was not. Notably, these discrepancies typically involved only small differences in SALT scores – consistent with the high ICC – and corresponded to borderline cases near the thresholds for mild or very severe AA. Additional information is provided in Files S4 and S5.

There were no clinically relevant differences in baseline characteristics between treatment groups in both the ITT and the FAS populations (Table 1; File S6). The mean age of patients was approximately 11 years. Half were experiencing their first episode of AA, while the remainder were in at least their second one, and one-quarter were in at least their third episode.

At randomization, the mean (SD) SALT score was 52.8 (26.2) in the total ITT population and 57.9 (21.2) in the total FAS population. At least 80% of the expected treatment solution was used by 77% of patients in the Cinainu arm and 92% of patients on placebo between randomization and Week 12, and by 64% and 70%, respectively, between Weeks 12 and 24.

Primary outcome – treatment period – full analysis set population

The adjusted mean relative change in SALT score from baseline to Week 24 was significantly higher in the Cinainu group than in the placebo group: adjusted mean difference (95% confidence interval) +26.3% (0.1–52.5); $P=0.0488$, Cohen's $d=0.52$ (Table 2). Rank-transformed analysis confirmed significance, and sensitivity analyses under varying missing data assumptions produced similar estimates. No baseline variables – including SALT score, age, disease duration – significantly modified the treatment effect (see File S6).

Secondary outcomes – treatment period – full analysis set population

The proportion of responders at Week 24 was significantly higher in the Cinainu group compared with the placebo group (26.2% vs. 5.0%; $P=0.048$) with a number needed to treat (NNT) of 4.7. The analysis of the absolute change in SALT score from baseline to Week 24 revealed a numerical difference favouring the Cinainu group but without reaching statistical significance (mean difference: +11.6%; $P=0.08$).

Table 1 Main baseline characteristics by population [intention-to-treat (ITT) population or full analysis set (FAS)]

	ITT		FAS	
Characteristics	**Cinainu (*n*=71)**	**Placebo (*n*=36)**	**Cinainu (*n*=42)**	**Placebo (*n*=20)**
Sex, *n* (%)				
Female	34 (48)	18 (50)	22 (52)	12 (60)
Male	37 (52)	18 (50)	20 (48)	8 (40)
Age; mean years (SD)	10.8 (4.2)	10.2 (4.5)	11.1 (3.8)	10.1 (4.0)
Median	11.0	11.0	11.5	9.5
Min–Max	2.0–17.0	2.0–17.0	4.0–17.0	3.0–17.0
Time since AA onset; mean years (SD)	3.2 (3.1)	2.8 (3.1)	3.3 (2.8)	2.5 (2.6)
Flares (current included); mean (SD)	1.9 (1.4)	1.9 (1.3)	2.0 (1.4)	2.0 (1.4)
AA severity at randomization; *n* (%)				
Mild[a]	21 (30)	10 (28)	–	–
Moderate	18 (25)	7 (19)	18 (43)	7 (35)
Severe	24 (34)	13 (36)	24 (57)	13 (65)
Very severe[b]	8 (11)	6 (17)	–	–
SALT score at randomization;[c] mean (SD)				
All patients	50.7 (25.1)	56.9 (28.1)	56.1 (21.1)	61.8 (21.4)
Moderate	36.0 (6.6)	37.6 (8.7)	36.0 (6.6)	37.6 (8.7)
Severe	71.2 (14.4)	74.8 (12.9)	71.2 (14.4)	74.8 (12.9)
AA in locations other than scalp; *n* (%)				
Eyebrows	55 (77)	28 (78)	31 (74)	15 (75)
Eyelashes	55 (77)	28 (78)	31 (74)	15 (75)
Nails	55 (77)	28 (78)	31 (74)	15 (75)
CDLQI score; mean (SD)	6.4 (5.8)	4.8 (5.2)	6.8 (6.2)	3.1 (4.0)
EQ-VAS score; mean (SD)	79.5 (17.2)	76.8 (22.8)	80.6 (18.7)	87.3 (12.4)
Country; *n* (%)				
Bulgaria	11 (15)	5 (14)	4 (10)	1 (5)
France	29 (41)	13 (36)	16 (38)	8 (40)
Germany	13 (18)	8 (22)	10 (24)	5 (25)
India	18 (25)	10 (28)	12 (29)	6 (30)

AA, alopecia areata (moderate, SALT score 25 to<50; severe, SALT score 50to <95); CDLQI, Children's Dermatology Life Quality Index; EQ-VAS, EuroQol Visual Analogue Scale; SALT, Severity of Alopecia Tool. [a]Patients classified as SALT<25 by either the investigator or the expert at randomization. [b]Patients classified as SALT>95 by either the investigator or the expert at randomization. [c]Based on investigator SALT assessments.

Treatment with Cinainu led to a significant improvement in QoL as measured by the CDLQI, with scores decreasing over time, indicating improved QoL. In contrast, placebo-treated patients experienced an increase in CDLQI scores, reflecting a decline in QoL (Figure 2c). These differences resulted in statistically significant and clinically relevant treatment effects in change in CDLQI score both at Week 12 and Week 24 with a moderate effect size: Cohen's d of 0.61 at Week 24 (Table 2). Similar statistically significant improvements were observed in the change in EQ-VAS scores with a moderate-to-large effect size: Cohen's d of 0.69 at Week 24 (Table 2).

Secondary outcomes – follow-up period – full analysis set population

Cinainu significantly improved SALT scores from baseline to Week 48, with a large adjusted mean between group difference of +39.4% (P=0.0033, d=0.80) in relative change (Table 2; Figure 2a). As an illustration, Figure 2b shows two patients, one of whom achieved a 39% relative improvement, and the other who achieved an 86% relative improvement, both at Week 48. The proportion of responders in the Cinainu group increased to 45.2% at Week 48 (placebo 15.0%; P=0.020, NNT=3.3). At Week 48, 47.6% of patients in the Cinainu group achieved a SALT score≤20 (placebo 15.0%; P=0.0129, NNT=3.1), and 35.7% reached a SALT score≤10 (placebo 10%; P=0.0339, NNT=3.9) (Table 2; Figure 2d).

Outcomes in the intention-to-treat population

Although treatment effects in the ITT population favoured Cinainu numerically (primary endpoint: +17.3%; P=0.35), they did not reach statistical significance. However, a significant quantitative interaction was observed between treatment and patient classification (FAS vs. non-FAS) for the primary endpoint (P=0.02), indicating that efficacy was significantly influenced by baseline disease severity (see File S5).

Safety

No serious AEs (SAEs) were reported in the Cinainu group compared with one SAE in the placebo group, which was considered to be unrelated to the study medication: vasovagal syncope resulting in hospitalization and full recovery. There was no difference in the incidence of TEAEs between patients treated with Cinainu or placebo (Table 3). AEs were local, transient, mild or moderate, except for one case of severe eczema of the face and the scalp in the Cinainu group that resolved after treatment discontinuation.

Discussion

In this phase II/III international, double-blind, placebo-controlled trial, Cinainu demonstrated statistically significant and clinically meaningful efficacy in children and

Table 2 Primary and secondary efficacy analyses in full analysis set population

	Cinainu		Placebo		Difference from placebo		
Continuous variable[a]	***n***	**Mean$_{adj}$ (SE)**	***n***	**Mean$_{adj}$ (SE)**	**Mean$_{adj}$ (95% CI)**	***P*-value**	**Cohen's d**
Endpoints at Week 24							
Relative CfB in SALT score	33	15.5% (7.9)	19	–10.8% (10.9)	26.3% (0.1–52.5)	0.0488	0.52
Absolute CfB in SALT score	33	9.3 (3.9)	19	–2.2 (5.4)	11.6 (–1.4 to 24.5)	0.081	0.46
SALT score	33	43.4 (4.3)	19	58.9 (6.0)	–15.5 (–29.9 to –1.2)	0.034	0.56
CfB in CDLQI	32	–2.0 (0.8)	17	1.0 (1.2)	–3.0 (–5.9 to –0.2)	0.039	0.61
CfB in EQ-VAS	27	3.3 (3.3)	12	–9.5 (5.2)	12.8 (0.3–25.3)	0.045	0.69
Endpoints at Week 48							
Relative CfB in SALT score	30	40.9% (7.6)	11	1.5% (11.1)	39.4% (13.1–65.6)	0.003	0.80
Absolute CfB in SALT score	30	23.7 (4.6)	11	0.7 (6.6)	23.0 (7.2–38.8)	0.004	0.77
SALT score	30	29.3 (4.8)	11	56.5 (6.8)	–27.2 (–43.4 to –11.0)	0.001	0.88
CfB in CDLQI	29	–2.6 (0.8)	12	1.4 (1.2)	–4.0 (–6.9 to –1.0)	0.0097	0.79
CfB in EQ-VAS	27	3.0 (3.4)	9	–5.2 (5.6)	8.2 (–5.0 to 21.4)	0.2163	0.43
Dichotomous variable[b]	***n***	**Responders (%)**	***n***	**Responders (%)**	**Rate difference (%)**	***P*-value**	**NNT**
Endpoints at Week 24							
Relative CfB ≥ 40% in SALT score	42	11 (26.2)	20	1 (5.0)	21.2	0.0484	4.7
Achieving a SALT score ≤ 20	42	11 (26.2)	20	2 (10.0)	16.2	0.143	6.2
Achieving a SALT score ≤ 10	42	10 (23.8)	20	2 (10.0)	13.8	0.198	7.2
Endpoints at Week 48							
Relative CfB ≥ 40% in SALT score	42	19 (45.2)	20	3 (15.0)	30.2	0.020	3.3
Achieving a SALT score ≤ 20	42	20 (47.6)	20	3 (15.0)	32.6	0.0129	3.1
Achieving a SALT score ≤ 10	42	15 (35.7)	20	3 (10.0)	25.7	0.0339	3.9

CDLQI, Children's Dermatology Life Quality Index; CfB, change from baseline; CI, confidence interval; EQ-VAS, EuroQol Visual Analogue Scale; Mean$_{adj}$, adjusted mean; NNT, number needed to treat; SALT, Severity of Alopecia Tool; SE, standard error. [a]For continuous outcomes, treatment effects were estimated using a mixed model for repeated measures (MMRM) with implicit imputation under the Missing at Random assumption; patient counts reflect only observed data at the analysed timepoint. [b]For binary outcomes, explicit imputation was applied as prespecified in the protocol, and patient counts reflect both observed and imputed data: patients with no post-baseline SALT score or who discontinued due to lack of efficacy or adverse events were classified as nonresponders; otherwise, last observation carried forward was used.

adolescents with moderate-to-severe AA in the predefined primary analysis population (FAS). The observed effect size for the primary endpoint was moderate (Cohen's d = 0.52), and responder rates yielded a clinically relevant NNT of 4.7. Cinainu also produced consistent improvements in QoL, with moderate-to-large effect sizes, sustained throughout the treatment-free follow-up period. Notably, treatment effects were increased by Week 48, with nearly half of Cinainu-treated patients achieving SALT scores ≤ 20. These sustained effects support a possible long-acting influence on the underlying immunopathology of AA.

Table 3 Summary of adverse events (AEs)

	Cinainu (*n* = 71)		Placebo (*n* = 36)	
Any of the following AEs	**Patients *n* (%)**	**Events**	**Patients *n* (%)**	**Events**
AEs	28 (39)	62	17 (47)	42
SAEs	0 (0)	0	1 (3)	2
TEAEs	28 (39)	58	17 (47)	38
TEAEs ≥ 5%				
Pyrexia (fever)	6 (8)	9	3 (8)	6
Alopecia areata	4 (6)	4	2 (6)	2
Cough	2 (3)	2	2 (6)	2
Acne	1 (1)	1	2 (6)	2
Eczema	5 (7)	5	3 (8)	3
Drug-related TEAEs	4 (6)	5	4 (11)	4
Severe TEAEs	1 (1)	1[a]	1 (3)	2[c]
Serious TEAEs	0 (0)	0	1 (3)	2[c]
TEAE leading to drug withdrawal	1 (1)	1[a]	0 (0)	0
TEAE leading to drug interruption	1 (1)[b]	1[b]	0 (0)	0
TEAE leading to death	0 (0)	0	0 (0)	0

SAE, serious AE; TEAE, treatment-emergent AE (an AE that occurs or worsens after the participant has started receiving the placebo or Cinainu). [a]Severe facial and scalp eczema. [b]Eczema. [c]Both TEAEs occurred in the same subject (Subject 20202); these events were initially reported as pharyngitis and subsequently clarified as vasovagal syncope following additional clinical information obtained during follow-up.

To date, no treatment is approved for moderate AA or for use in children with this condition. The evidence supporting topical therapies in paediatric AA remains limited, primarily comprising case series and a few small trials. There were only two randomized controlled trials, both in mild AA,[38] a population distinct from that targeted in the RAAINBOW study. With regard to systemic treatment, oral JAK inhibitors are approved for severe AA in adolescents and adults,[18–20] but they have not demonstrated sustained efficacy after discontinuation[21] and are associated with potentially serious AEs.[39] In contrast, RAAINBOW findings support Cinainu as a potential option for children and adolescents with moderate-to-severe AA and also for an effective and safe maintenance therapy following oral JAK inhibitor response.

Although 45 of the 107 ITT patients were excluded from the FAS population, the ITT principle and the randomization were preserved in the FAS population and the FAS adheres to the criteria defined in the European Medicines Agency ICH E9 guideline for its use as the primary analysis population.[40] Specifically, the FAS included patients based on prerandomization SALT scores (25–95), determined independently of treatment and defined prior to unblinding to avoid bias. All patients in the FAS were analysed regardless of treatment compliance. Baseline characteristics were similar across treatment groups and the 2 : 1 randomization ratio was maintained.

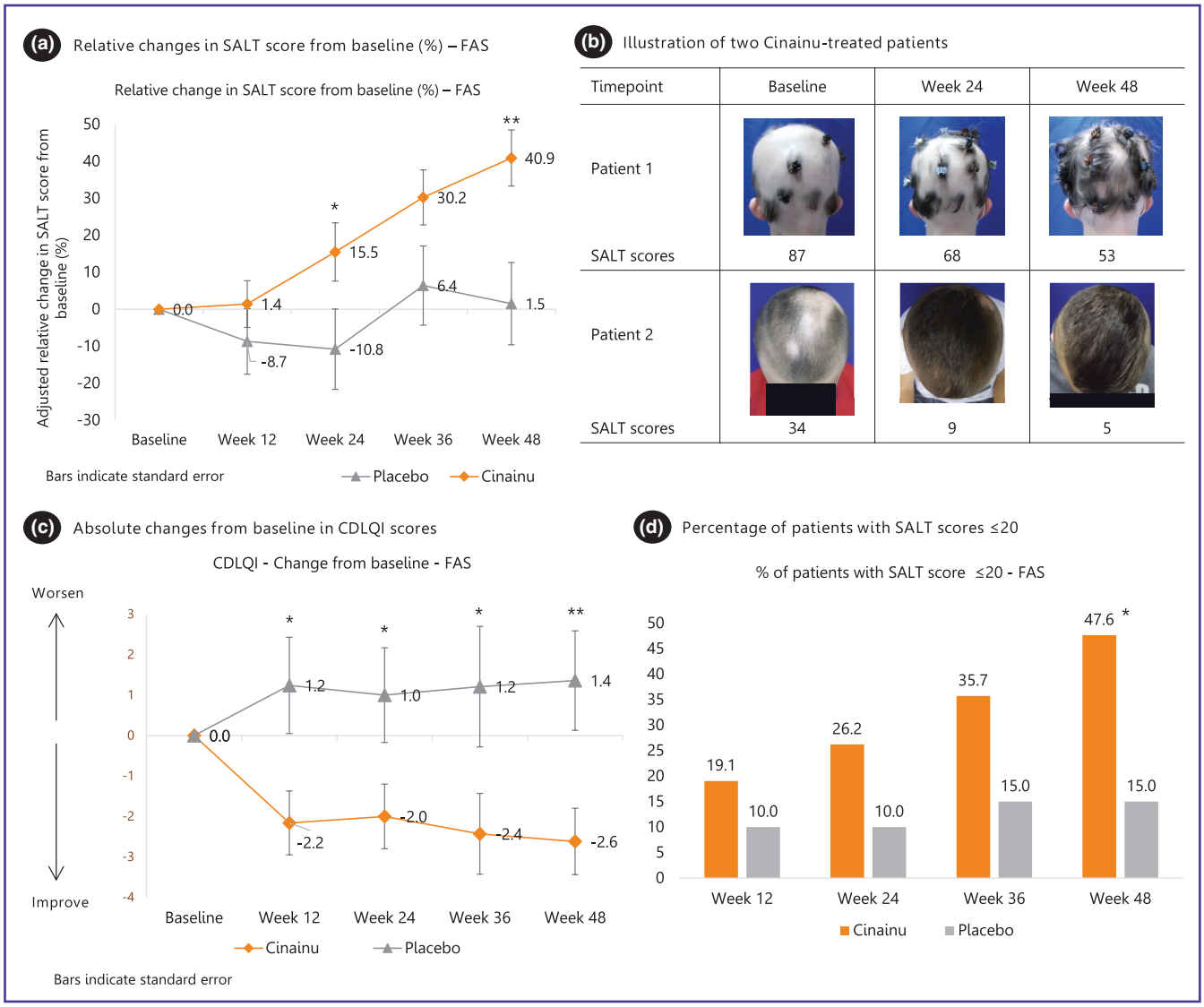


Figure 2 (a) Relative changes from baseline in SALT score (FAS). (b) Two Cinainu-treated patients. Patient 1: disease duration 9 years, with 1 relapse; 39% change in SALT score from baseline to Week 48. Patient 2: disease duration 2 years; 86% change in SALT score from baseline to Week 48. (c) Absolute changes from baseline in CDLQI scores. (d) Percentages of patients (FAS) with SALT scores ≤20 at each visit. CDLQI, Children's Dermatology Life Quality Index; FAS, full analysis set; SALT, Severity of Alopecia Tool. *$P<0.05$; **$P<0.01$.

The significant interaction between treatment and patient classification (FAS vs. non-FAS), along with the positive effects observed in the FAS, indicates that the treatment effect was not uniform and that the null hypothesis of treatment equality was rejected in the ITT population. While the direction of effect was consistent, the magnitude was smaller and not statistically significant in patients with mild AA. However, the study was not designed or powered to detect effects in this subgroup, where spontaneous improvement is common and room for treatment benefit is limited (see File S5).[34–36] Moreover, RAAINBOW findings suggest that adopting the recently revised threshold for mild AA (SALT < 20 instead of < 25)[41] may reduce assay sensitivity in future trials targeting moderate disease.

The dropout rate was 16% at the end of the treatment period in the FAS population, but the sensitivity analysis using various imputation methods provided similar estimates as the primary analysis, supporting a low risk of bias due to missing data.

Finally, Cinainu was well tolerated. Its safety was consistent with the safety profile of the four GRAS plants used in its composition. RAAINBOW tolerability and safety results were also consistent with the results from previous studies on other hair disorders with 578 patients exposed to the active substance Cinainu, including 108 for a period of 12 months.[25,28,29]

In conclusion, in the RAAINBOW study, Cinainu showed efficacy, safety and sustained benefits during follow-up in children and adolescents with moderate-to-severe AA, a population with significant unmet needs.

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Author contributions

Data acquisition, interpretation, revision of the draft manuscript: Ulrike Blume-Peytavi, Bianca Maria Piraccini, Pascal Reygagne Data analysis and interpretation: Julien Guiraud, Saad Harti, Jiawei Liu, William Pralong, Alexandre Guichard Conception and drafting of the manuscript: Saad Harti, Ulrike Blume-Peytavi, Julien Guiraud, and Fabienne Péretz (Abelia Science) Statistical analyses: Julien Guiraud, Bhaswati Mukherjee.

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Conflicts of interest

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Data availability

For any request, please contact Saad Harti (Legacy Healthcare, Route de la Corniche 3B, 1066 Epalinges, Switzerland; s.harti@legacyhealthcare.ch).

Ethics statement

An independent ethics committee approved the protocol. Prior written informed consent signed by parent(s)/legally authorized representative and assent/consent signed by the patients (if applicable) were obtained for each patient before inclusion in the study.

Patient consent

Written informed consent for publication was obtained by parent(s)/legally authorized representative and by the patients (if applicable).

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

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