Coacillium 22,25% cutaneous solution

Phase 2/3 registration study in children and adolescents with moderate to severe alopecia areata (RAAINBOW)

An international, double-blind, placebo-controlled, randomised, multi-centre study

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Disclosures

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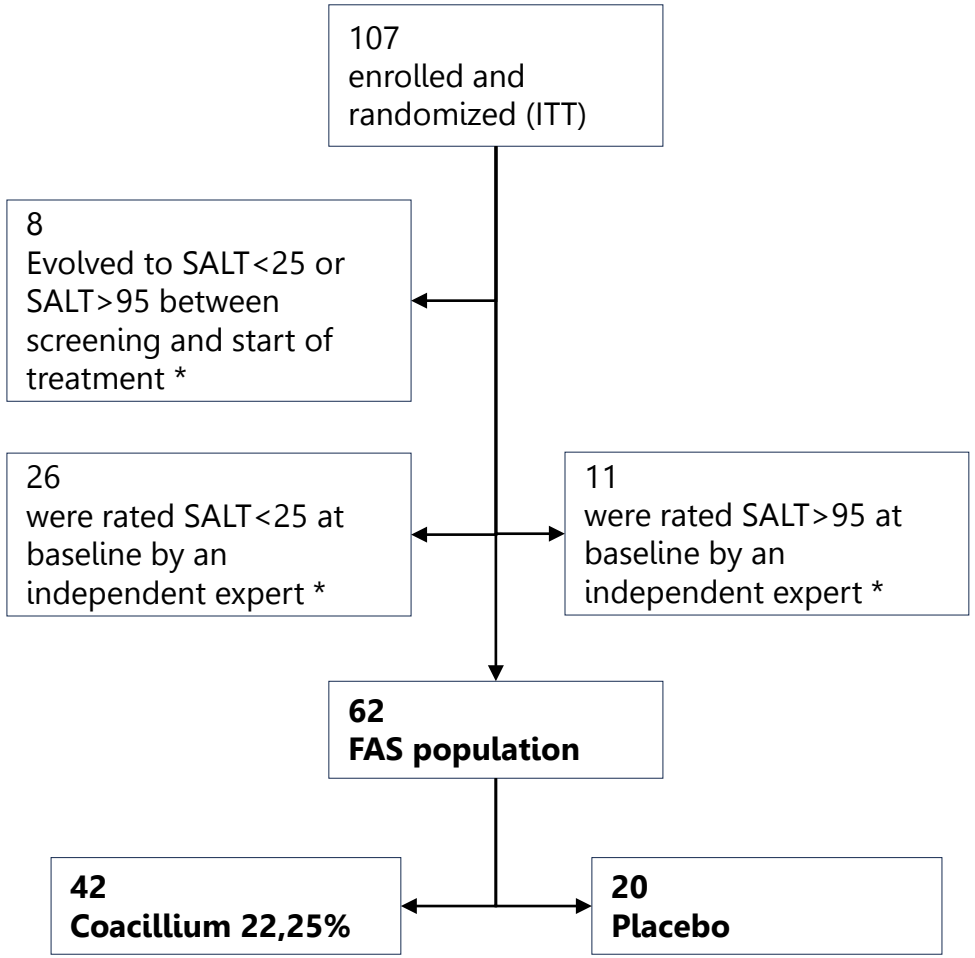
Remaining key unmet needs in Alopecia Areata

- An approved drug with which benefit/risk profile allows treatment of children
- An approved drug which benefit/risk profile allows early intervention
    - when disease is still moderate, to prevent progression to a severe stage
    - after first manifestation in infancy, to possibly prevent disease chronicity
- An approved drug which discontinuation does not lead to rapid disease relapse
- An approved drug which safety provides confidence for long-term compliance
- A topical drug which ease of use supports compliance

Coacillium in moderate to severe alopecia areata in children and adolescents
Baseline demographics

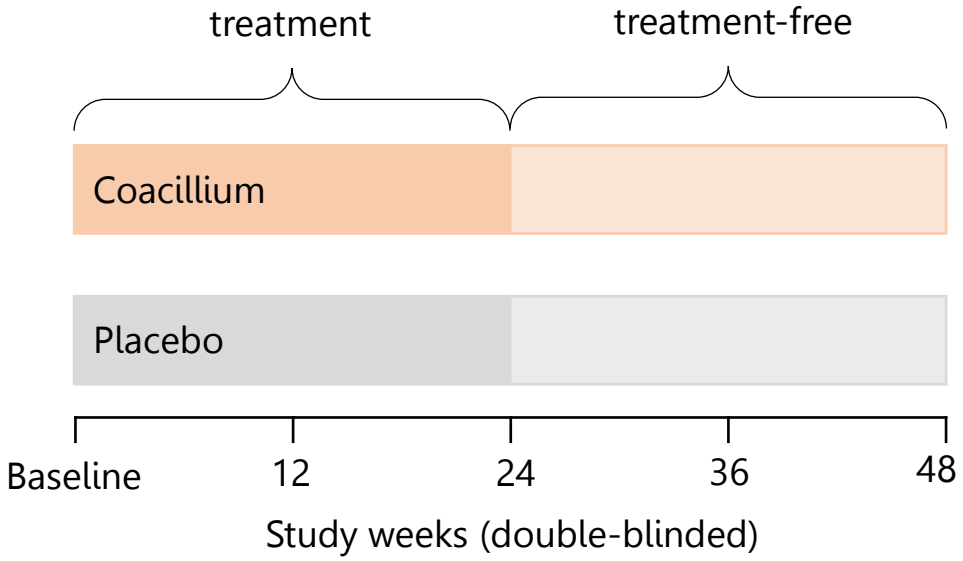


Item	Total	Coacillium	Placebo
N (ITT)	107	71 (66%)	36 (34%
N (FAS)	62	42 (68%)	20 (32%)
Completers at week 48 n (%)	41 (66%)	30 (71%)	11 (55%)
Severe	37 (60%)	24 (57%)	13 (65%)
Moderate	25 (40%)	18 (43%)	7 (35%)
Average SALT at V1	58	56.1	61.8
Average age	11	11.1	10.1
Time since onset of AA	3 years	3.3 years	2.5 years
Female	34 (55%)	22 (52%)	12 (60%)
Patients in their 1st flare of AA	32 (52%)	21 (50%)	11 (55%)
Patients with several flares	30 (48%)	21 (50%)	9 (45%)

* All exclusions from FAS population were decided before unblinding

Coacillium in moderate to severe alopecia areata in children and adolescents
Trial design

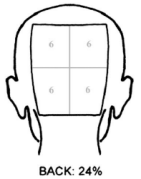
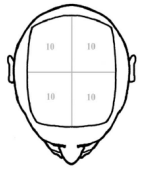
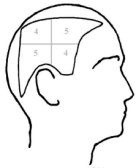
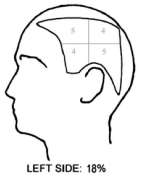
EMA requested a treatment-free follow-up of 6 months to assess disease relapse after treatment discontinuation



Primary and key 2ry endpoints were analysed at 24 weeks.

No concomitant treatment for AA was allowed

The SALT score is a weighted sum of the percentage of hair loss in the 4 quadrants of the scalp, ranging from 0 (no hair loss) to 100 (complete hair loss)

			
 BACK: 24%	 TOP: 40%	 RIGHT SIDE: 18%	 LEFT SIDE: 18%
24% * 55%	40% * 95%	18% * 90%	18% * 95%
13.2%	38%	16.2%	17.1%
SALT score 84.5% (13.2% + 38% + 16.2% + 17,1%)			

SALT scoring example (adapted from Olsen 2004)

* SALT = Severity of ALopecia Tool. 1. Olsen et al. J Am Acad Dermatol. 2004 Sep;51(3):440-7.

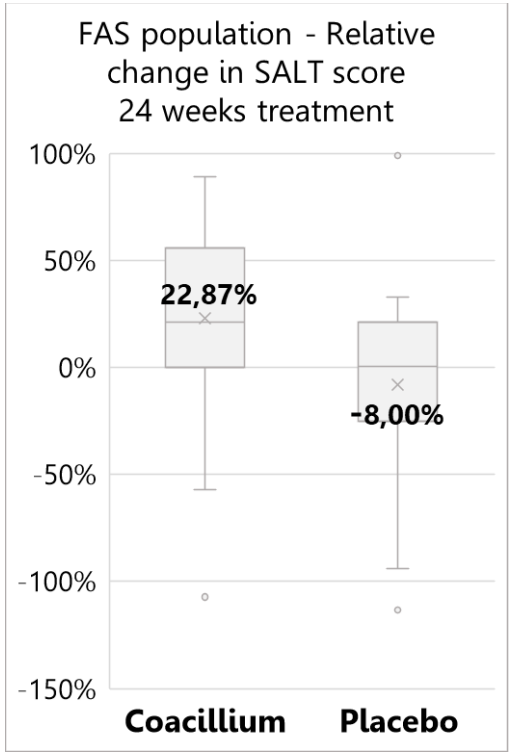
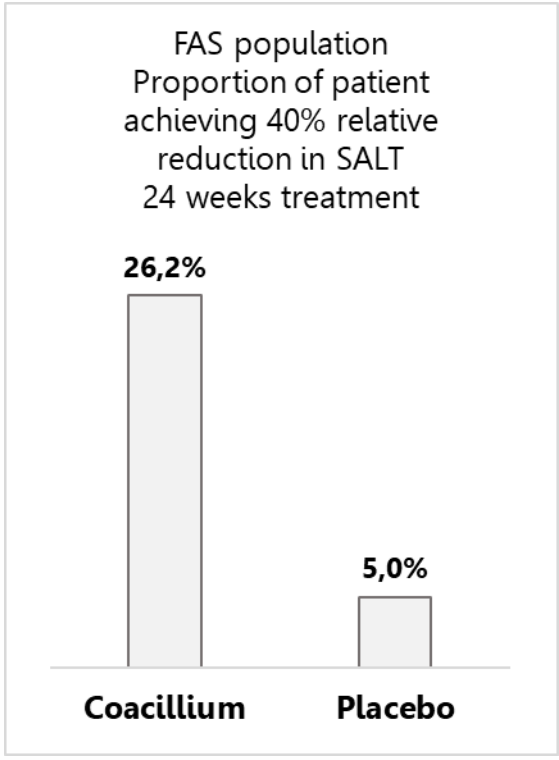
Coacillium in moderate to severe alopecia areata in children and adolescents
Efficacy endpoints

Per protocol	
1ry	Relative change in SALT after 24 weeks of treatment
2ry	Absolute change in SALT after 24 weeks of treatment
	Proportion of subjects achieving at least a 40% relative reduction in SALT after 24 weeks treatment
Other*	Duration of treatment effect from Visit 3 (end of treatment) after 12 weeks (Visit 4) and 24 weeks (Visit 5) of treatment-free period
	Effect on hair follicles in non-alopecic areas by quantifying the number of new alopecic areas
	Change in CDLQI and EQ-VAS

Post-hoc analysis
Percentage of patients achieving SALT ≤ 20
Percentage of patients achieving SALT ≤ 10

* selection

Coacillium in moderate to severe alopecia areata in children and adolescents
Primary and key secondary endpoints were met

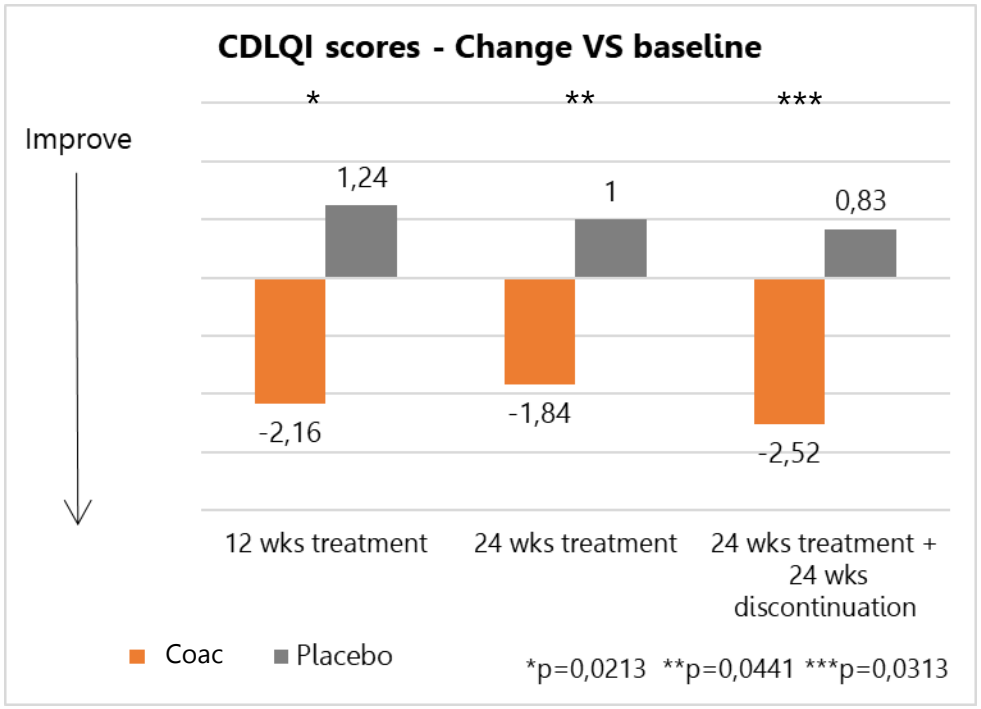
Relative change in SALT after 24 weeks of treatment	Subjects achieving at least 40% relative reduction in SALT
Treatment effect = 31%	**26% achieved relative reduction in SALT > 40%**
 p <0,0001	 p = 0,0484
Change was also superior in ITT population (p<0,0001)	

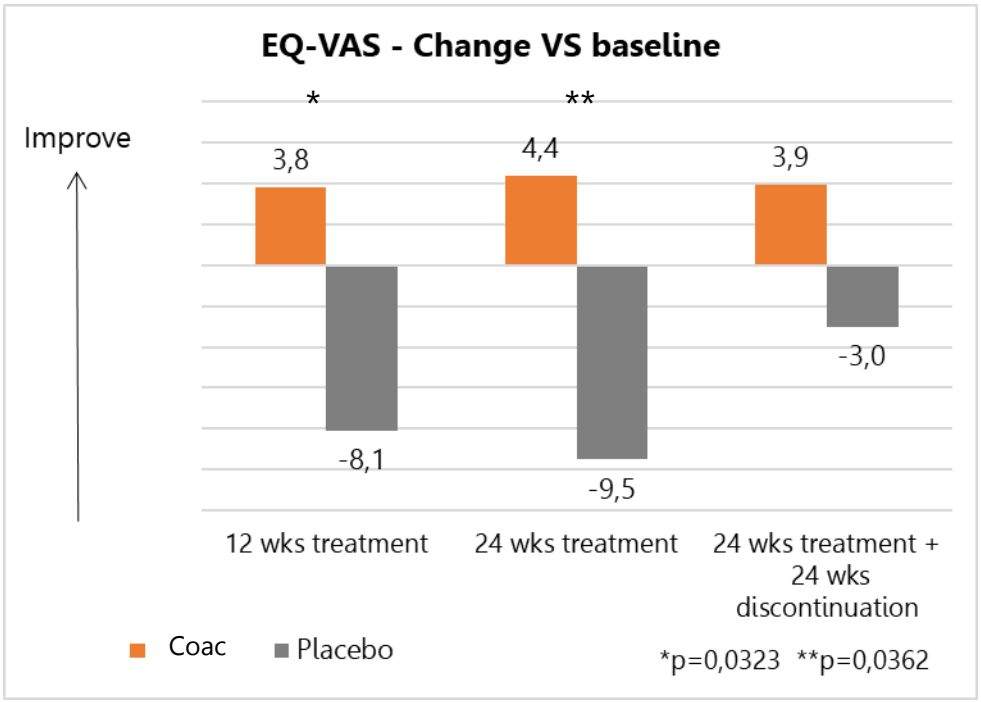
Coacillium in moderate to severe alopecia areata in children and adolescents
Efficacy was positively correlated with improved quality of life

Improvement in QoL endpoints is consistent with treatment effect, in both CDLQI and EQ-5D Y endpoints

Patients express improvement in QoL as early as after 12 weeks treatment

Expressed improvement maintains after 24 weeks of treatment discontinuation





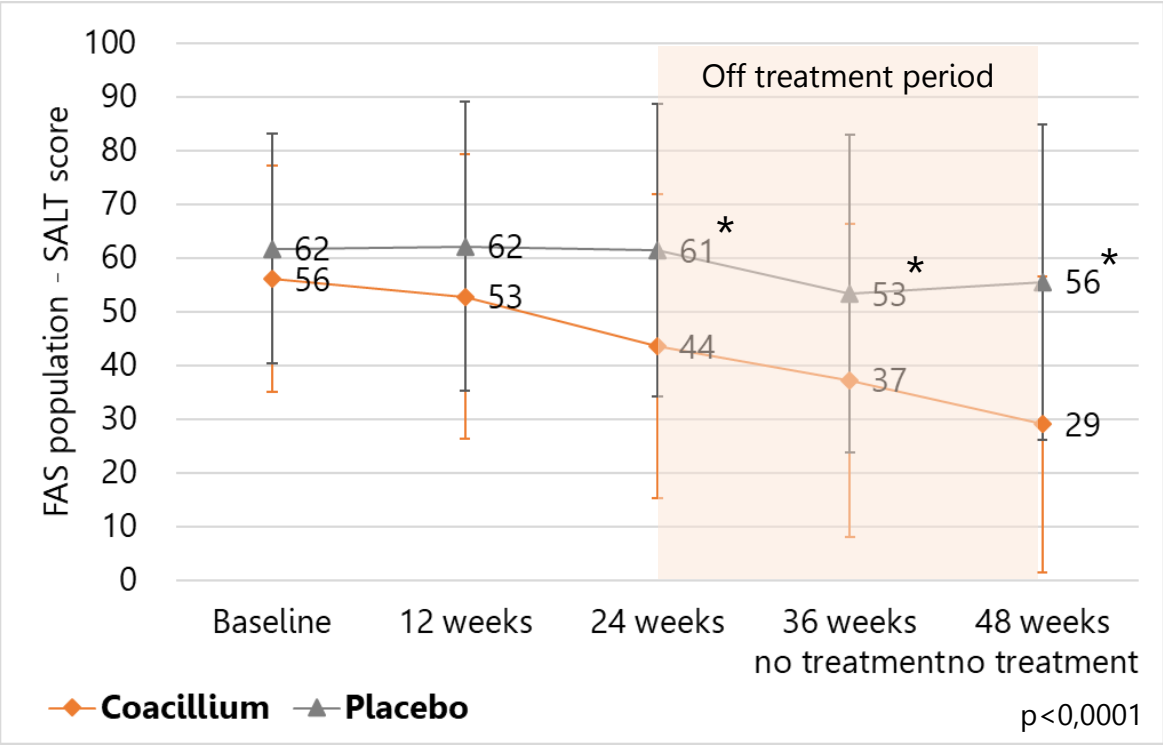
Note: CDLQI and EQ-5D Y are not specific to AA

Coacillium in moderate to severe alopecia areata in children and adolescents
Durable and continued response after treatment discontinuation

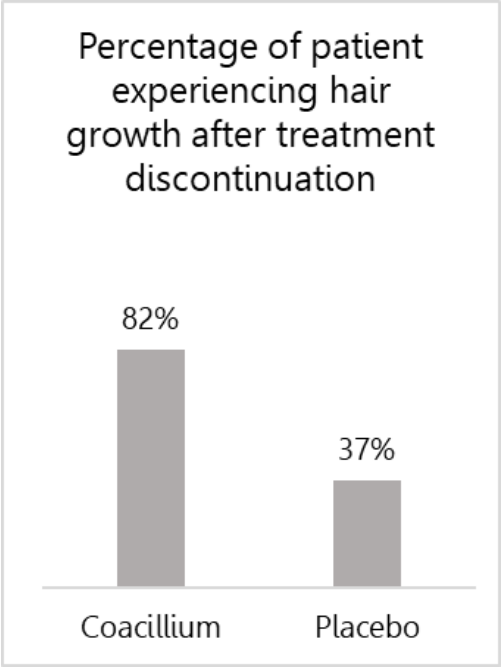
After 24 weeks, treatment is discontinued

After discontinuation, SALT score is measured after 12 weeks (week 36) and 24 weeks (week 48)

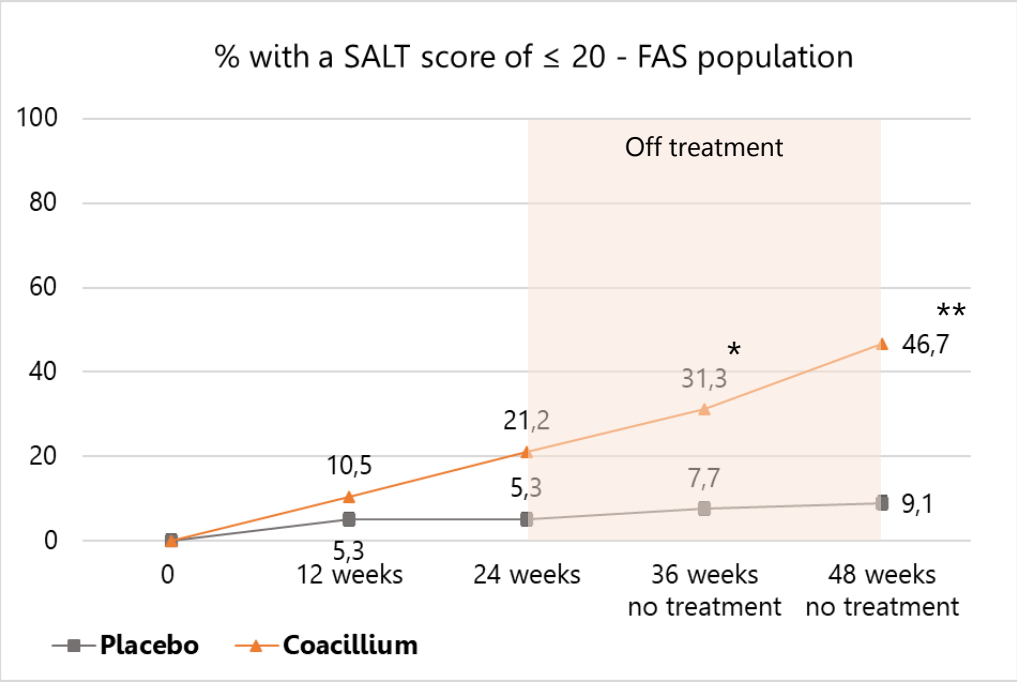
After Coacillium discontinuation, SALT continues to improve, from 44 to 29



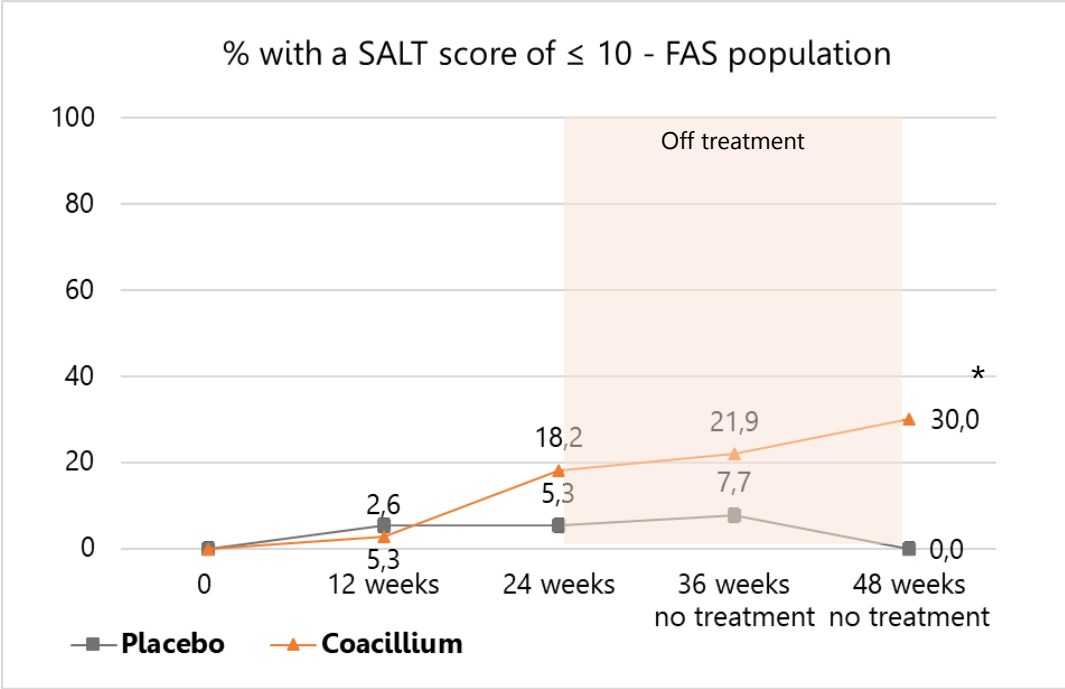
82% of Coacillium group experienced hair growth during the treatment-free follow-up versus 37% in placebo group



Coacillium in moderate to severe alopecia areata in children and adolescents
Nearly half of patients reached SALT ≤ 20, and a third reached SALT ≤ 10



* p=0,0453 ** p=0,0031



* p=0,0065

FAS population (n)	Baseline	12 weeks	24 weeks	36 weeks	48 weeks
Coacillium	42	38	33	32	30
Placebo	20	19	19	13	11

Coacillium in moderate to severe alopecia areata in children and adolescents

Average SALT change for treatment responders to Coacillium was 41%

Visit	Timeline	SALT	Top	Posterior	Left side	Right side
V1	Baseline	**60**				
V3	After 24 weeks treatment	**33**				
V5	24 weeks after discontinuation of treatment	**8**				

Patient with 45% change during treatment period, representative of the mean

Coacillium in moderate to severe alopecia areata in children and adolescents
Safety and tolerability

Adverse Events (AEs) in RAAINBOW trial

Characteristics	Coacillium (N=71)		Placebo (N=36)	
	n %	E	n %	E
Any AEs	28 (39.4%)	62	17 (47.2%)	42
Any SAEs	**0**		**1 (2.8%)**	**2**
Any TEAEs	28 (39.4%)	58	17 (47.2%)	38
Drug-related TEAEs	4 (5.6%)	5	4 (11.1%)	4
Severe TEAEs	1 (1.4%)	1	1 (2.8%)	2
Serious TEAEs	0		1 (2.8%)	2
TEAEs Leading to Drug Withdrawn	1 (1.4%)	1	0	
TEAEs Leading to Drug Interruption	1 (1.4%)	1	0	
TEAEs Leading to Death	0		0	

[1] Percentages are computed using N provided in the Column header.

[2] AE: Adverse Event, TEAE: Treatment Emergent Adverse Event, n: Number of subjects; E- Number of Events

TEAE correspond to eczema, skin irritation mainly. All mild, moderate and transient
Severe TEAE is Acute eczema scalp and face

No drug-related Serious AEs

One severe TEAE (acute eczema*)

Others are local, mild-moderate, transient

* Treatment was interrupted. Acute eczema stopped
Children and adolescents with AA are more likely to have atopic dermatitis, eczema (17.4% vs. 2.2% controls) (Conic, 2020).

Coacillium in moderate to severe alopecia areata in children and adolescents
Composition and route of administration explain safety

Coacillium is a topically-applied, liquid, cutaneous solution

It contains 4 plant extracts classified as GRAS (Generally Regarded As Safe):

- Allium cepa
- Citrus limon
- Theobroma cacao
- Paullinia Cupana

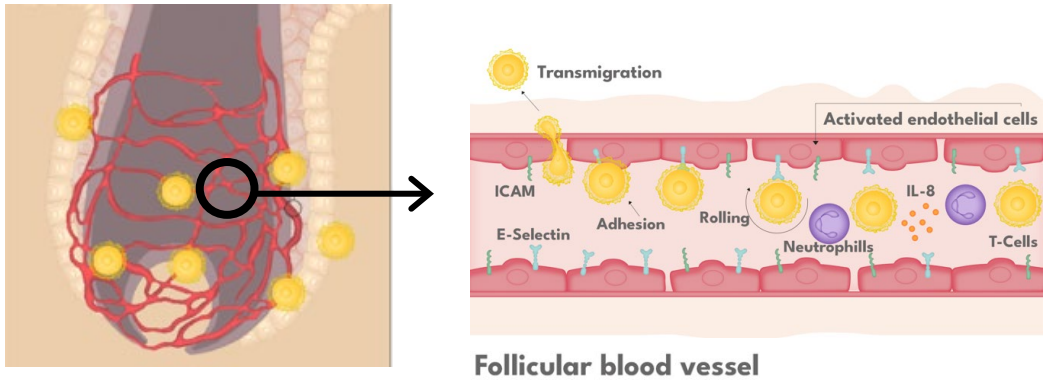
Coacillium is regulated by EMA/FDA prescription Botanical drug status*

* https://www.fda.gov/regulatory-information/search-fda-guidance-documents/botanical-drug-development-guidance-industry
* https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products

Coacillium in moderate to severe alopecia areata in children and adolescents

Pleitropic mode of action explains efficacy

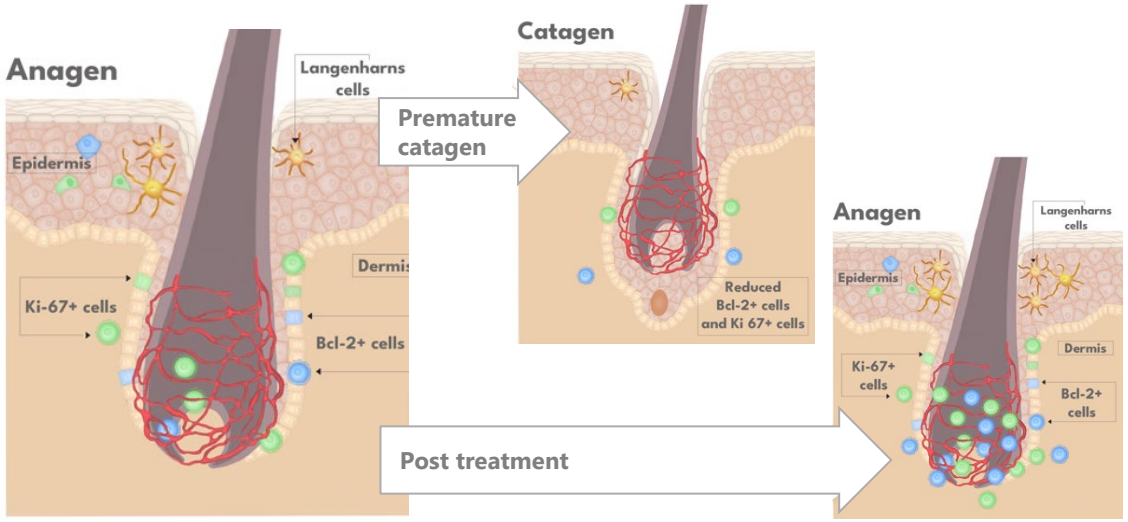
Effect on Immune Privilege (IP) collapse



Adhesion molecules expressed by activated endothelial cells (EC) are essential for extravasation of immuno-inflammatory cells, a process believed to cause hair follicular IP collapse. Activated ECs are obligate interaction partners for T cells tissue-residency.

Coacillium reduces expression of pro-inflammatory adhesion molecules ICAM-1, E-selectin & the T-cell chemotaxin il-8 (by HUVEC) [1] suggesting attenuation of EC activation.

Effect on apoptotic pathway



Significant cytotoxic T cell infiltrate and signaling molecules cause excessive apoptosis. Impaired clearance of apoptotic cells is believed to be directly linked to autoimmune diseases. The dysregulated apoptotic process leads hair follicles (HFs) to forcibly enter into catagen phase, a critical indication of IP collapse in AA development.

Analysis on scalp biopsy of subjects with androgenetic alopecia reveals that Coacillium restores Bcl-2 expression in HF cells [2] towards the level identified in healthy subjects [3], preventing premature onset of catagen. The observed improved expression of Ki-67 in HF cells [2] represents a strong signal of enhanced cell survival capacity, indicating higher number of active cycling cells. The detected increased density of CD1A+/Langerhans [2] cells in epidermis is essential for immune tolerance in scalp skin.

1. Bourget N. et al., 2014 (Internal report). 2. Cucé L et al. 2011; Surg Cosmet Dermatol 3(2):123-28.. 3. Cucé L et al. 2012 (Internal report).

Coacillium in moderate to severe alopecia areata in children and adolescents
Conclusion

- In this phase 2-3 trial involving children and adolescents with moderate to severe alopecia areata, Coacillium cutaneous solution 22.25% twice-daily was superior to placebo after 24 weeks of treatment
- Coacillium was well tolerated
- Most Coacillium responders experienced durable response after treatment discontinuation
- Coacillium is the first drugs to show sustained remission off-treatment in alopecia areata, safely
- Coacillium might be a suitable treatment option for children and adolescents with moderate to severe AA
- Larger trials will allow better understand response to treatment

Coacillium in moderate to severe alopecia areata in children and adolescents

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