Coacillium 22,25% cutaneous solution

RAAINBOW Phase 2/3 registration study in children and adolescents (2-18 years old) with moderate to severe alopecia areata (SALT score 25-95)

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

U Blume-Peytavi, BM Piraccini, P Reygagne, B Mukherjee, A Guichard, J Liu, W Pralong, S Harti

Authors and Disclosures

Ulrike Blume-Peytavi, Bianca Maria Piraccini, Pascal Reygagne, Bhawasti Mukherjee, Alexandre Guichard , Jiawei Liu, William Pralong, Saad Harti

Ulrike Blume-Peytavi / Abbvie, Amryt, Bayer, Boots Healthcare, Cantabria Labs, Cassiopeia, CeraVe, Concert Pharmaceuticals / Sun Pharma Dermocosmétique Vichy, Galderma Laboratorium GmbH, Lilly, Laboratoires Bailleuil, Legacy Healthcare, LEO-Pharma, Novartis, Pfizer, Sanofi Regeneron

Bianca Maria Piraccini / Almirall, Difa Cooper, Dercos-L'Oreal, Lilly, ISDIN, Legacy Healthcare, Pierre Fabre-Ducray, Pfizer

Pascal Reygagne / BMS, Concert pharmaceutical, L'Oreal research, Lilly, Novartis, Pfizer, Vichy Laboratoires

Bhawasti Mukherjee / Employed by CliniExperts Research Services Pvt. Ltd

Alexandre Guichard, Jiawei Li, William Pralong, Saad Harti / Employees and consultants for Legacy Healthcare

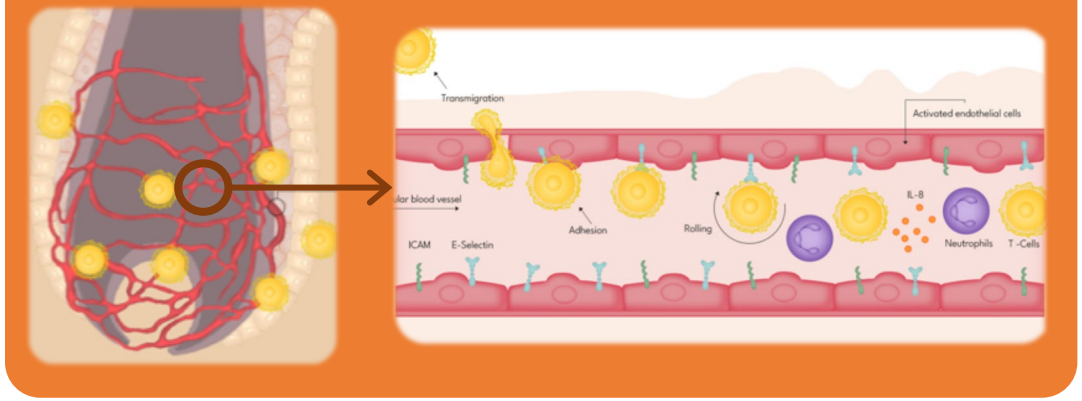
Coacillium overview

Regulatory status	Composition	Form and administration	Development rationale
Coacillium is a prescription botanical drug "Botanical drug" status was established in 2004 by FDA and FDA To allow the development of novel prescription drugs based on plants extracts	Coacillium contains 4 plants' extracts All 4 plants are classified as GRAS (Generally Regarded As Safe): ▪ Allium cepa ▪ Citrus limon ▪ Theobroma cacao ▪ Paullinia cupana	▪ Liquid solution ▪ Spray form ▪ Scent-free ▪ Fast absorbing ▪ No residue  Application to whole scalp allows ▪ treatment of lesions ▪ prevention of new lesions	Coacillium plants extracts contain multiple molecules and metabolites, allowing a pleiotropic mode of action on several targets, simultaneously Coacillium plants are known safe for human use, ensuring clean-safety profile Therefore, Coacillium was allowed to be evaluated in children, before adults

Pleitropic mode of action

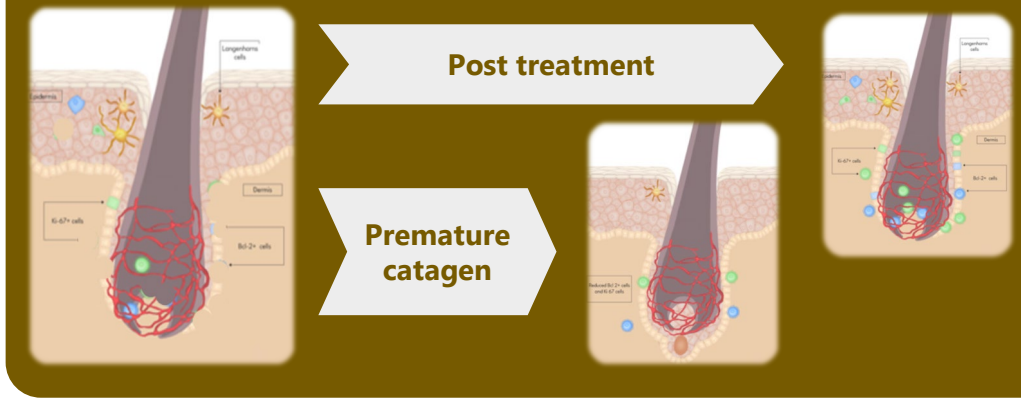
Although the mechanism of Coacillium action is not conclusively defined, it was shown to have the following actions

Effect on Immune Privilege (IP) collapse



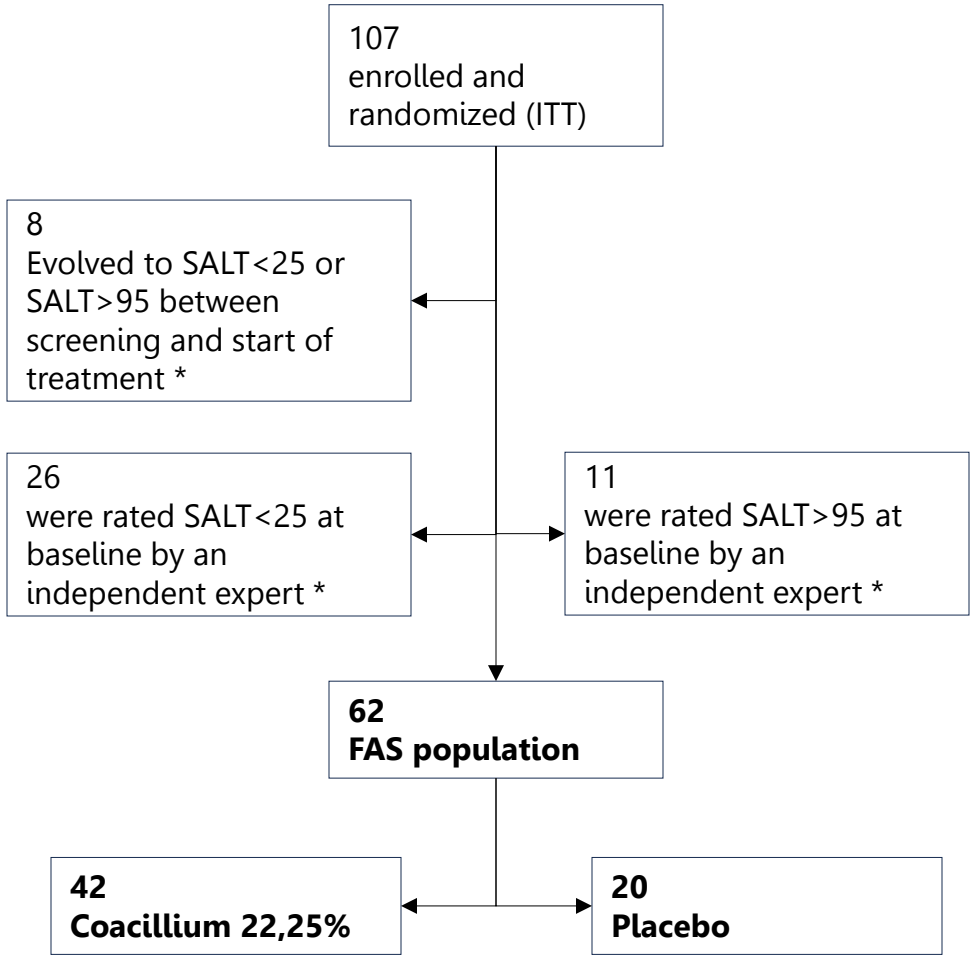
Coacillium reduces expression of pro-inflammatory adhesion molecule ICAM-1, E-selectin, & IL-8, preventing extravasation of immune cells into the hair follicle (HF)

Effect on apoptotic pathway



Coacillium prevents the premature onset of catagen driven hair loss by restoring Bcl-2 expression in HFs in addition to increasing the expression of Ki-67 in HF cells

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%)

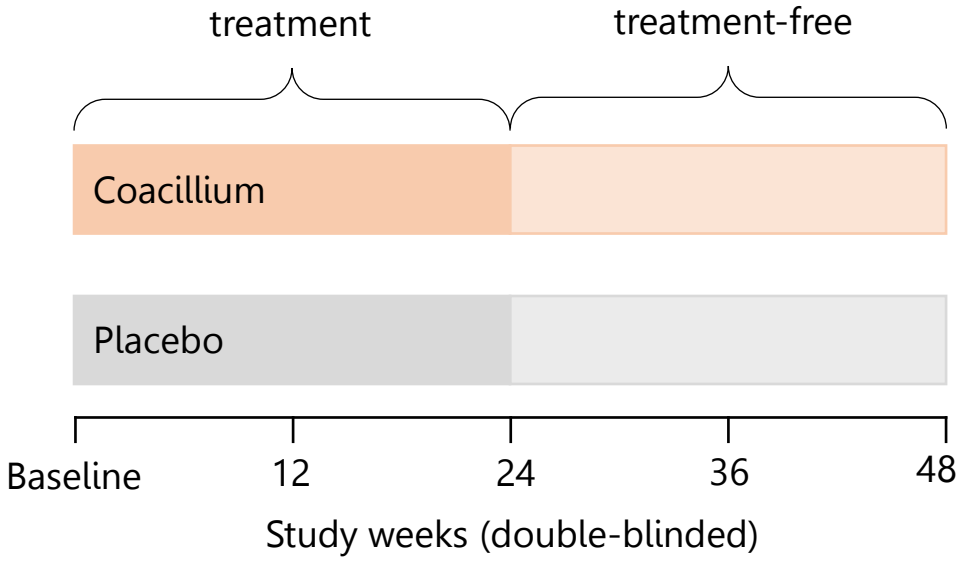
ITT - Patients rated SALT 25-95 by investigator only at enrollment
FAS - Patients rated SALT 25-95 by investigator AND independent expert at start of treatment (V1)

The primary analysis population was the FAS. The analysis of the primary endpoint was also repeated in the ITT population.

* All exclusions from FAS population were decided before unblinding

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

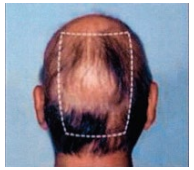
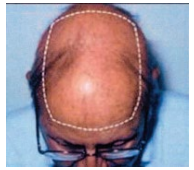
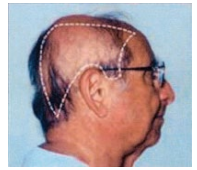
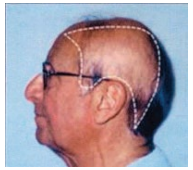
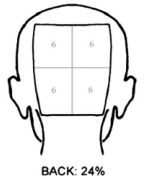
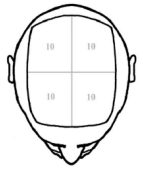
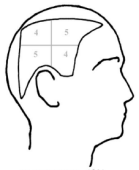
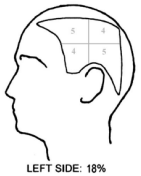
EMA requested a treatment-free follow-up of 6 months to assess disease relapse after treatment discontinuation



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

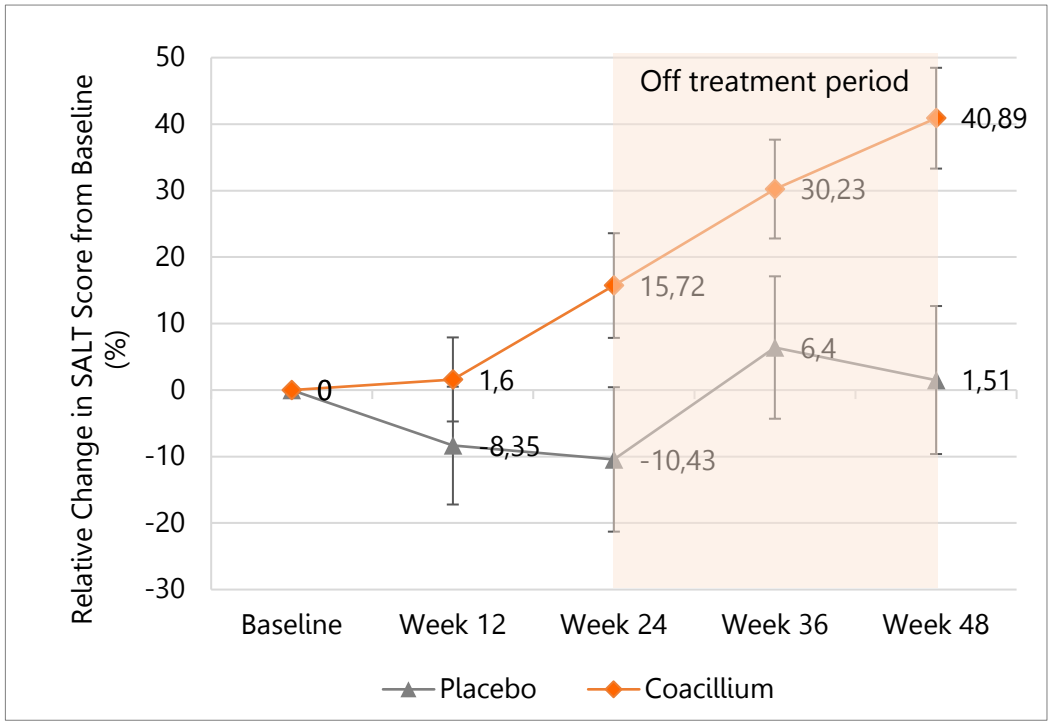
Per protocol	
1ry	Relative change in SALT after 24 weeks of treatment
2ry	Absolute change in SALT after 24 weeks of treatment
	Proportion of subjects achieving at least a 40% relative reduction in SALT after 24 weeks treatment
Other*	Relative change in SALT after 48 weeks
	Number of new alopecic areas
	Change in CDLQI and EQ-VAS

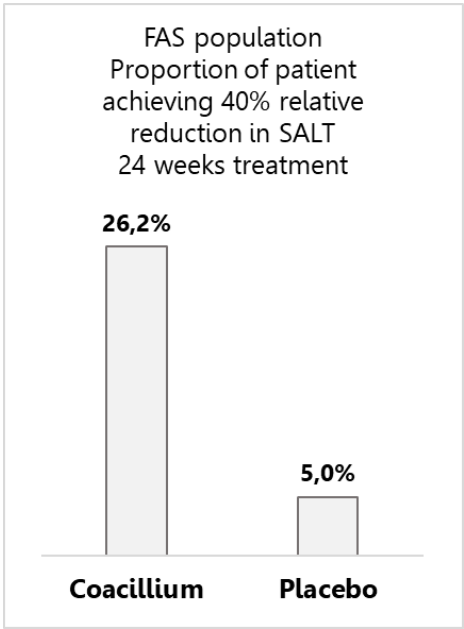
Post-hoc analysis
Percentage of patients achieving SALT ≤ 20
Percentage of patients achieving SALT ≤ 10

* selection

Coacillium in moderate to severe alopecia areata in children and adolescents
Primary endpoints was met

Relative change in SALT after 24 weeks of treatment	Subjects achieving at least 40% relative reduction in SALT
Treatment effect at **week 24 = +26.31%** (p=0,0488) Treatment effect at **week 48 = +39.37%** (p=0,0033)	**26% achieved relative reduction in SALT > 40%**





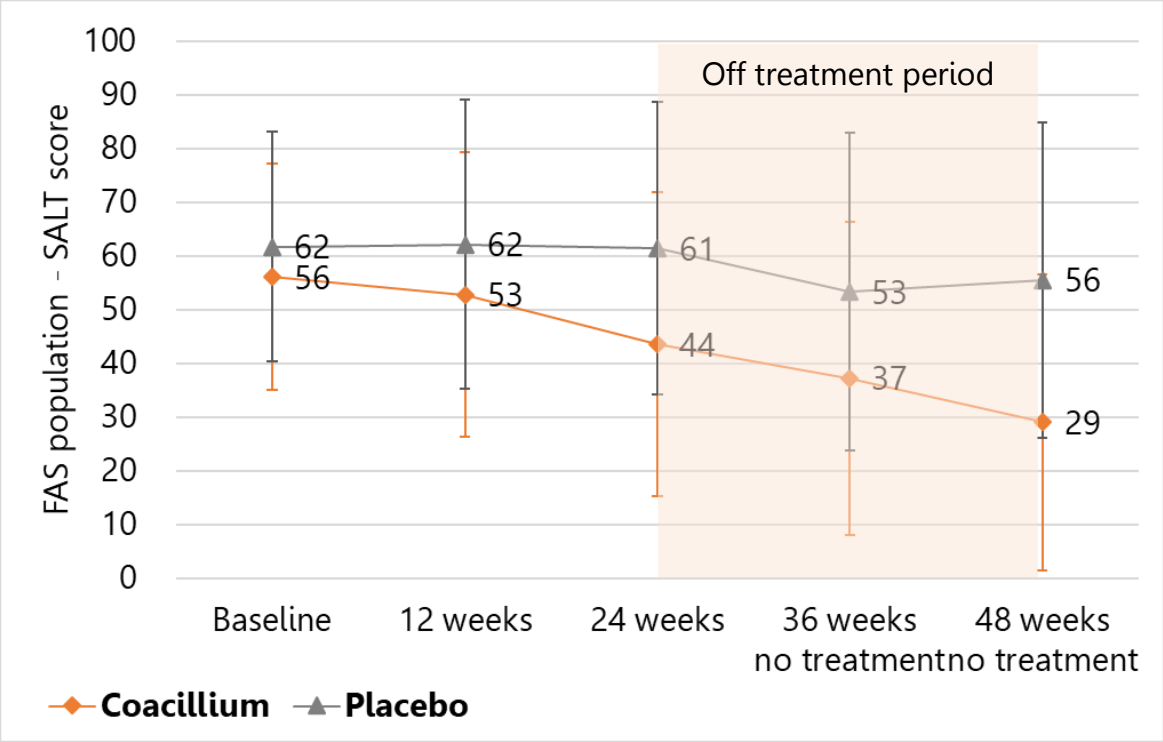
p = 0,0488

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

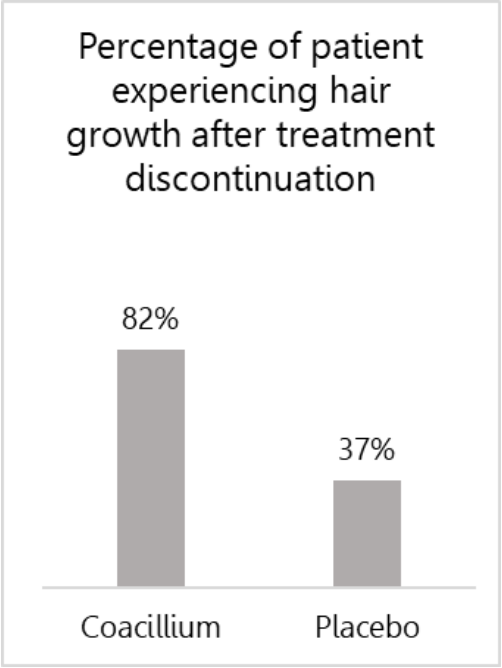
After 24 weeks, treatment is discontinued

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

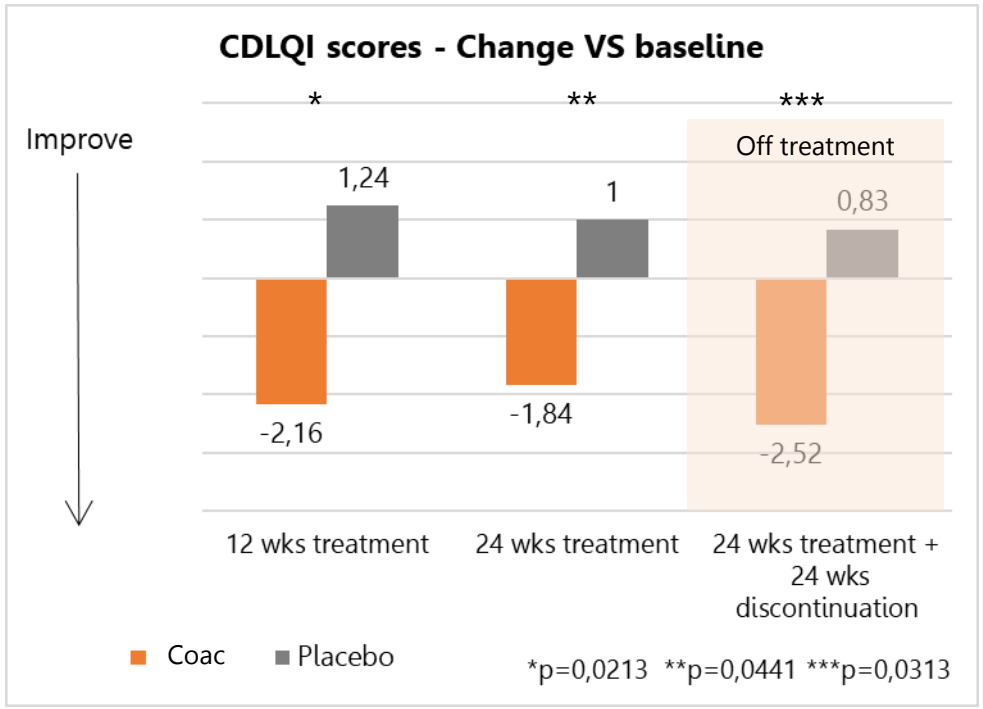


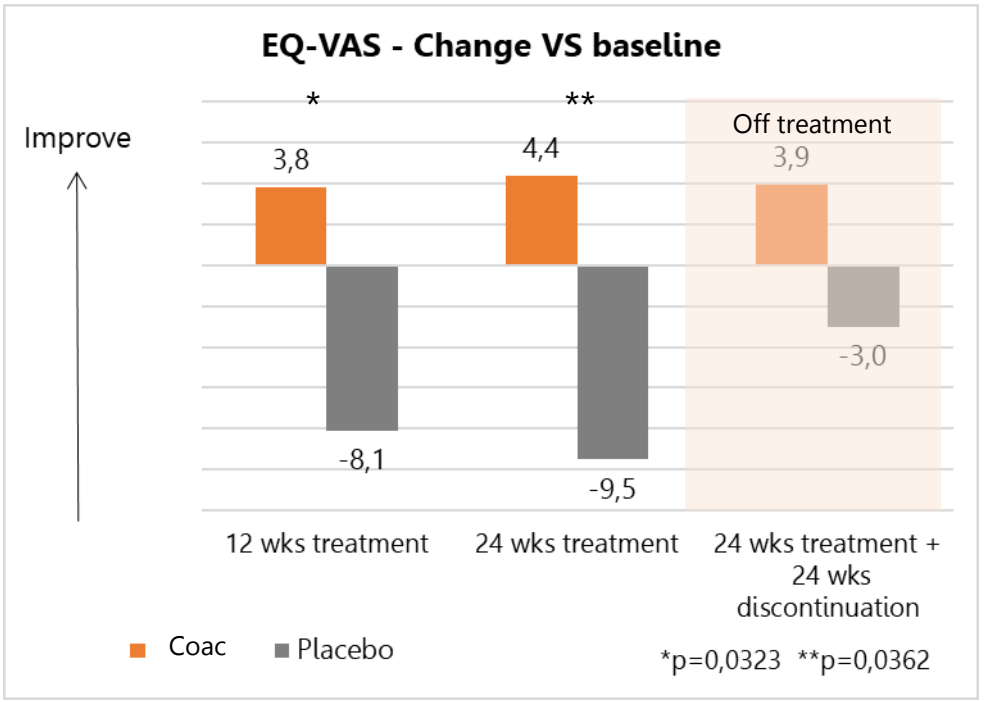
Coacillium in moderate to severe alopecia areata in children and adolescents
Efficacy was positively correlated with improved quality of life

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, supporting compliance

Expressed improvement maintains after 24 weeks of treatment discontinuation

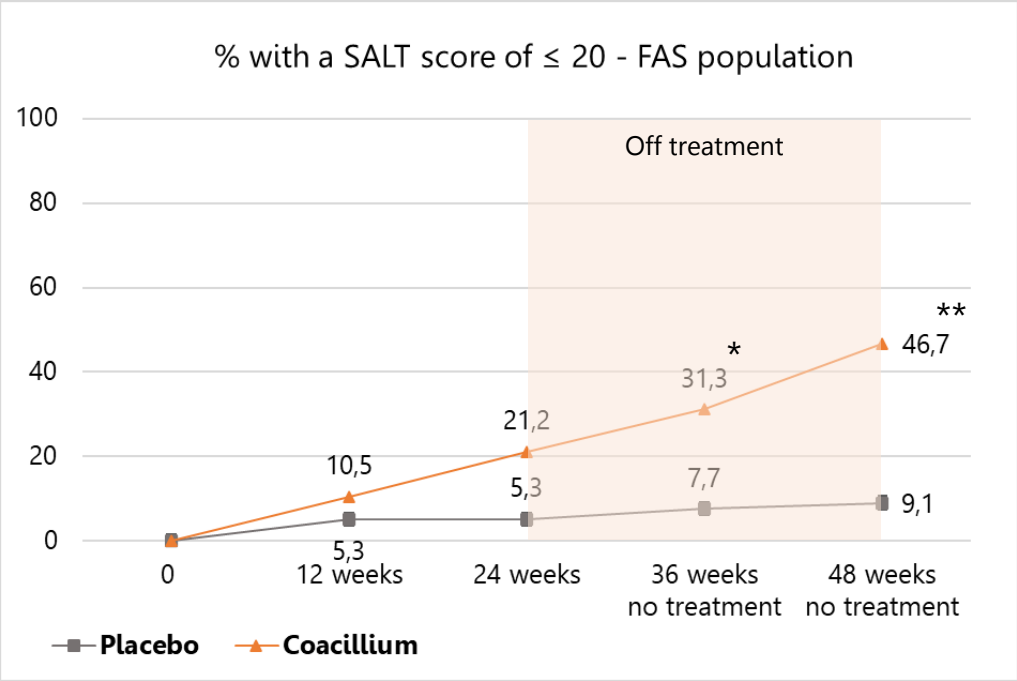




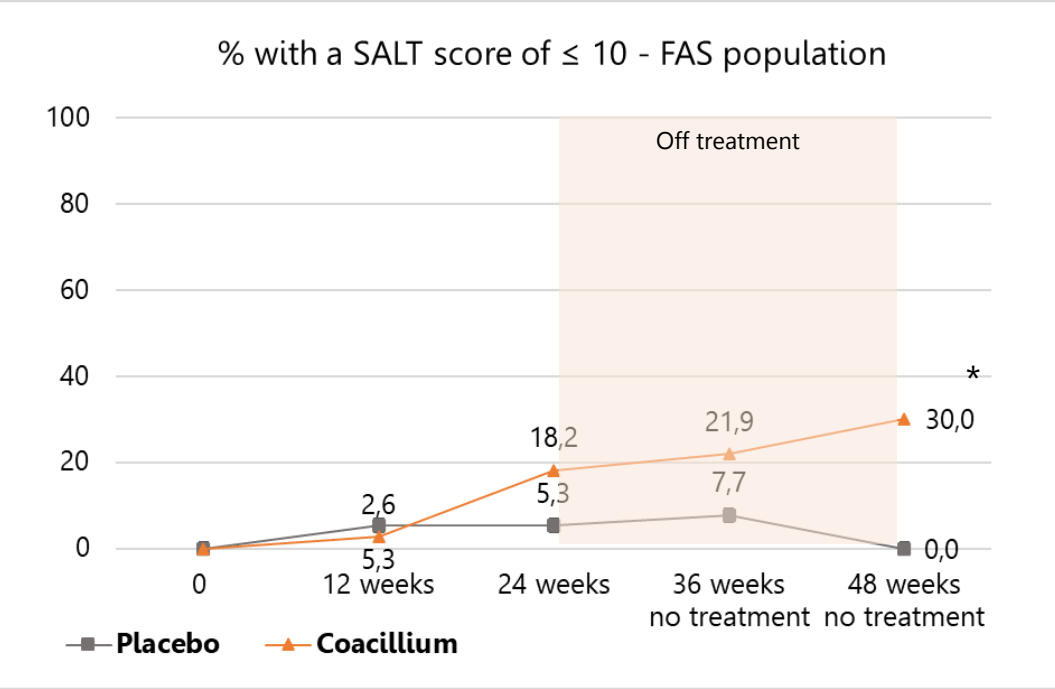
Note: CDLQI and EQ-5D Y are not specific to AA

Coacillium in moderate to severe alopecia areata in children and adolescents

Nearly half of patients reached SALT ≤ 20, and a third reached SALT ≤ 10



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

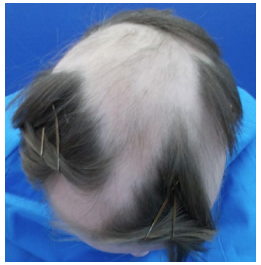
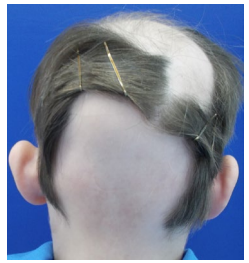
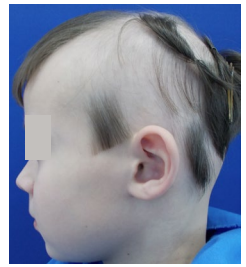
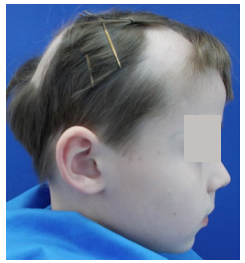
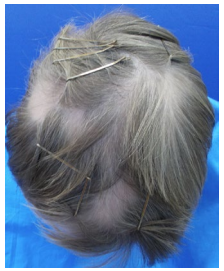
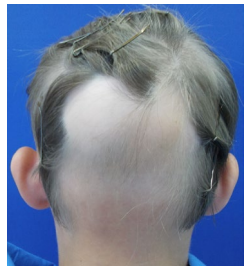
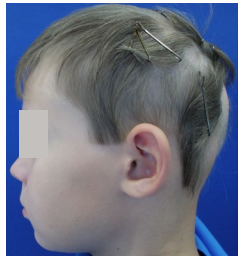
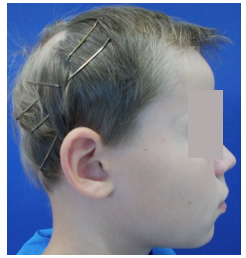
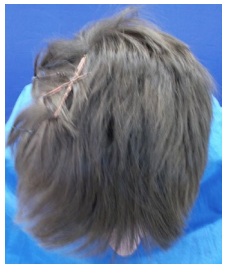
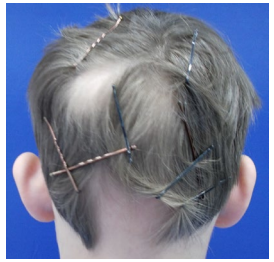
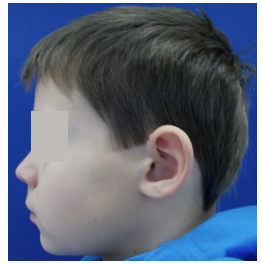
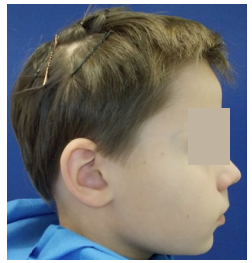


* p=0,0065

Coacillium in moderate to severe alopecia areata in children and adolescents

Average SALT change for treatment responders to Coacillium was 41%

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

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**				

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
Conclusion

- Phase 2-3 trial involving children and adolescents with moderate to severe alopecia areata
- 24-weeks treatment of Coacillium cutaneous solution 22.25% twice-daily was superior to placebo
- After treatment discontinuation most Coacillium responders experienced durable response (24 week-follow-up period)
- Coacillium well tolerated, with no immunosuppressant effects
- Coacillium first drug to show sustained remission off-treatment in an autoimmune-mediated disease without immune-altering side-effects
- Coacillium suitable treatment option for children and adolescents with moderate to severe AA
- Larger trials needed to better understand response to treatment