

# A Botanical Compound for the Treatment of Alopecia Areata and Chemotherapy-Induced Alopecia



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Legacy Healthcare has developed and patented a topical botanical with a unique mechanism of action, an extensive clinical data package, and excellent safety from the 2.2 million units already sold, all of which has enabled it to enter late-stage clinical development for alopecia areata (AA), chemotherapy-induced alopecia, and soon female androgenetic alopecia. As this drug candidate is very safe, the European Medicines Agency agreed to Legacy Healthcare's request to initiate late-stage clinical trial first in children, the neediest population suffering from AA. The initial trend from the phase II/III trial conducted to assess the efficacy and safety of the drug candidate in pediatric AA (RAAINBOW trial) looks promising, although no conclusions can be made. This drug candidate seems to offer several potential safety and economic advantages over other investigational synthetic and biologic compounds currently being investigated in populations with AA overall and especially for children.

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## Introduction

Alopecia areata (AA) is an autoimmune disease that targets the hair follicles, and its onset can occur during childhood or adulthood. In the United States, approximately 500,000 individuals have AA (Safavi, 1992). At present, there is no approved treatment for AA. Off-label use of compounds such as minoxidil is common, and there are active on-going clinical investigations of a variety of different therapies, including but not limited to corticosteroids, calcineurin inhibitors, and immunotherapies such as Jak inhibitors.

The recent Food and Drug Administration (FDA) patient-focused drug development meeting and the current literature on quality of life concerns for patients with AA have indicated that (1) product safety may be almost as important as efficacy, given the fact that cure for the disease may be elusive with a very long-term use of a treatment rule;

and (2) drug cost cannot be ignored, and there are limitations on how much patients might be willing to pay out of pocket if there were a lapse in insurance coverage, particularly if the treatment would only control the disease as opposed to cure (Beikert et al., 2014; FDA, 2018; Okhovat et al., 2017).

Chemotherapy-induced alopecia (CIA) is an acquired form of hair loss and certainly the most visibly distressing side effect of administration of cytotoxic chemotherapy. As with AA, there is no FDA-approved medication for the treatment of CIA, although scalp cooling before administration of chemotherapy appears to have some preventative effect (Dunnill, 2018).

Legacy Healthcare is a Swiss biopharmaceutical company that is focused on the development of innovative botanical drugs in oncology supportive care and dermatology. The first new botanical entity developed by Legacy Healthcare is Cellium, a

patented blend of four nonsynthesized botanical extracts known to be safe for human use. These botanicals are *Allium cepa* (onion), *Citrus limon* (lemon), *Paullinia cupana* (guarana), and *Theobroma cacao* (cocoa). Botanical Drugs are a novel regulatory pathway established by the FDA and the European Medicines Agency (EMA), allowing innovative drugs to be developed from full botanical extracts rather than mono-molecule synthetic compounds or biologics.

Cellium is currently marketed respectively as a topical consumer hair care product and is being investigated as a botanical drug for AA and CIA. The proposed mechanism of action of Cellium at the skin level is three-fold. First, Cellium normalizes resistance to apoptosis and restores (before 3 months) the number of cells expressing Bcl-2 in subjects with AGA to levels close to those observed in healthy controls. Second, Cellium has been reported to have an anti-inflammatory action: there is a significant increase (74%) in Langerhans cells in the epidermis, which modulates the immune response and increases its anti-inflammatory function (Trueb, 2015). Finally, Cellium increases collagen content and remodeling: collagen around the hair follicle is increased by almost 80%, and when remodeled, the collagen fibers are thicker. Multiple proofs of concept studies of Cellium in subjects with alopecia have been successfully completed and published.

## Efficacy and safety data on cellium

Cellium is currently in phase II/III testing for pediatric AA in Europe and phase II testing in Switzerland and Japan for the CIA. The most-advanced on-going clinical trial is the RAINBOW study for pediatric AA, a randomized, double-blind placebo-controlled study versus placebo in 100 children and adolescents with moderate to severe AA. The study subjects are being evaluated in 14 sites in Germany, France, Bulgaria, Romania. RAINBOW has been approved by the EMA as a phase II/III trial, based on the National Alopecia Areata Foundation Uniform Core Protocol. The main criteria of

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evaluation will be the relative change in the Severity of Alopecia Scores (SALT) from Baseline using visual assessment and globally standardized scalp photographs. The SALT score indicates the sum area of the scalp with hair loss and ranges from 0–100 (minimum-maximum), with higher scores indicating more hair loss. A negative change in the SALT score indicates lesser (improvement) hair loss, whereas high positive scores indicate more (worsening) hair loss. There will also be the patient reported outcome and QOL questionnaires. The full protocol consists of 6 months of treatment and 6 months of treatment-free follow-up.

In July 2019, we conducted a first interim blinded-review of the data from the first 12 subjects who completed the full protocol (corresponding to two blocks of randomization), to decide whether or not the trial should continue or be discontinued in case no trend of efficacy is observed. The randomization ratio being 2:1, we know that 8 of the 12 subjects were provided with the drug candidate and 4 with the placebo. The outcome is the following: (1) six improved (variation of SALT score from –63% to –97%), (2) four remained stable (variation of SALT score from of –20% to 7%), (3) one worsened (variation of SALT score from of 107%), and (4) one dropped-out after the first visit (note: a negative % means there was an improvement in the SALT score [i.e., reduction of alopecia]).

See [Supplementary Materials](#) for data on an additional 36 subjects not included in our July 2019 study.

**Discussion**

Although no conclusion can be drawn in any manner because the data are blinded, the trend might be considered promising because spontaneous improvement in moderate to severe AA is low (Vestey and Savin, 1987). In addition, no side-effects were reported, as we expected from the excellent safety observed from the 2.2 million units already sold (side effect lower than 1 in 100,000 units sold, and minor only—such as redness).

Contrary to New Chemical Entities or New Biological Entities, which cannot be made available until their final approval, the safety profile of certain botanical drugs enables them to be made available as consumer products with no drug claim while their development as a drug is ongoing, enabling collection of real-world evidence of safety data. This new drug approval pathway represents a complete shift in the access paradigm.

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**CONFLICT OF INTEREST**

SH is the President of Legacy Healthcare. BP is a consultant for Legacy Healthcare.

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**AUTHOR CONTRIBUTIONS**

Writing - Original Draft Preparation: BP, SH; Writing - Review and Editing: BP, SH

**SUPPLEMENTARY MATERIAL**

Supplementary material is linked to the online version of the paper at [www.jidonline.org](http://www.jidonline.org), and at <https://doi.org/10.1016/j.jisp.2020.04.009>.

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