Legacy Healthcare Updates on Regulatory Focus for Cinainu in Europe, US and Japan

March 28, 2025, Epalinges, Switzerland

Legacy Healthcare expands its efforts to advance regulatory discussions with National Health Authorities in Europe, U.S. Food and Drug Administration (FDA) and Japan Pharmaceuticals and Medical Devices Agency (PMDA). This in part reflects the company's decision to withdrawal its marketing authorization application (MAA) for Cinainu following the outcome of the centralized assessment procedure with the European Medicines Agency (EMA).

Cinainu has demonstrated positive efficacy and safety results in its pivotal Phase 2/3 trial (RAAINBOW) on children and adolescents with moderate to severe alopecia areata conducted under an EMA-approved Paediatric Investigation Plan (PIP). The study met its primary endpoint in the predefined Full Analysis Set (FAS), and in 2023, the EMA's Paediatric Committee (PDCO) issued a positive opinion confirming full compliance of the development program with the agreed PIP.

During the centralized assessment procedure, the Committee for Medicinal Products for Human Use (CHMP) adopted a position that diverged from the scientific and procedural framework established through the EMA-agreed PIP and endorsed by the PDCO. Key elements of the development strategy—including the primary analysis population (FAS) and non-clinical requirements—were not accepted by the CHMP, despite having been formally agreed earlier in the regulatory process. The FAS, which had been explicitly accepted by the PDCO and formed the basis for the study's primary efficacy outcome, aligns with established ICH and EMA guideline criteria for use as primary analysis population. The rationale provided by the CHMP for not accepting the FAS was based on considerations that are not reflected in ICH or EMA guidelines and, in the Company's view, lack scientific justification.

The CHMP's stance on non-clinical data was equally unexpected. Cinainu is composed of botanical extracts from onion, lemon, guarana, and cacao—plants with a long history of safe human use. In addition, over 600 patients were exposed to the product in clinical trials and 100 million daily doses commercialized as cosmetic-status lotion, with no reported safety concern. As part of the PIP approval process, involving the PDCO and other EMA committee and working groups, it was concluded that no additional non-clinical studies were required. The CHMP's subsequent request for long-term toxicity and carcinogenicity studies therefore stands in clear contradiction with the earlier scientific conclusions formally endorsed by EMA.

This divergence resulted in a CHMP opinion issued on November 14, 2024, which does not reflect the development plan agreed with EMA or the data generated in accordance with it.

In addition, although the CHMP raised concerns related to Cinainu's herbal composition, the Herbal Medicinal Products Committee (HMPC)—EMA's designated expert body for herbal medicinal products—was not consulted, despite its foreseen role in such assessments. Further limitations in the evaluation process were observed during the re-examination phase, where key regulatory documents, including the PIP and PDCO opinions, were not shared with the ad-hoc expert group.

In light of these circumstances, Legacy Healthcare concluded that the conditions for a consistent and coherent regulatory assessment were no longer in place. The Company therefore made the strategic decision to withdraw its MAA and formally requested the retraction of the CHMP opinion and related public documentation.

"Cinainu's development was conducted in full alignment with the regulatory guidance established through the EMA-agreed Paediatric Investigation Plan. We stand by the clinically meaningful efficacy demonstrated in the RAAINBOW study and remain fully committed to advancing Cinainu toward market approval, particularly in the United States," said Saad Harti, CEO of Legacy Healthcare.

The Company is making public both the Withdrawal Letter and Follow-Up Letter submitted to EMA, which outline in detail the rationale for this decision and provide additional context on the regulatory process.

In addition to starting National Health Authorities consultations in Europe, the company continues its interaction with FDA in the US and PMDA in Japan pursuing approval for Cinainu.

About Cinainu

Cinainu is a topical drug candidate composed of four botanical extracts (onion, citrus, guarana, cocoa) with a well-established safety profile, designed to treat children and adolescents suffering from moderate to severe alopecia areata. Over 100 million daily doses have been commercially used worldwide in non-prescription settings, and over 600 patients have been exposed to Cinainu in different clinical trials, up to 12 months, with no reported safety concern.

About Legacy Healthcare

Legacy Healthcare is a Swiss-based biopharmaceutical company focused on leveraging the pleiotropic activity and safety profile of plants known safe for human use to develop prescription botanical drugs that address serious medical conditions. The company's first product candidate, Cinainu, has demonstrated strong safety and efficacy in a phase 2/3 study involving patients suffering from alopecia areata, a chronic autoimmune condition with highly damaging psycho-social issues that impact all who suffer from it, especially children.

For more information about Legacy Healthcare please visit www.legacyhealthcare.ch

For inquiries: contact@legacyhealthcare.ch

26 February 2025

To : EMA Executive Director
CHMP Chair
European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam, The Netherlands

Ref: CINAINU cutaneous solution
Centralized Marketing Authorization Application - Withdrawal
Submission sequence number: 0011
Reference number: EMEA/H/C/0004155/0000

Dear EMA Executive Director, Dear CHMP Chair,

Legacy Healthcare (France) SAS, the Applicant, hereby notifies the EMA of the withdrawal of the Marketing Authorization Application (MAA) of CINAINU cutaneous solution. CINAINU is composed of extracts from four plants (onion, lemon, guarana, cocoa) and was proposed for the treatment of moderate to severe alopecia areata in children and adolescents.

On November 14, 2024, the CHMP issued a negative opinion on Cinainu MAA. The CHMP clinical and non-clinical grounds for refusal are in direct contradiction with the EMA-approved Paediatric Investigation Plan (PIP) for Cinainu and the positive opinion from the EMA Paediatric Committee (PDCO) confirming compliance with the agreed PIP. Furthermore, despite the CHMP raising quality-related concerns, the Committee on Herbal Medicinal Products (HMPC), EMA's designated expert body for herbal medicinal products, was never consulted during the CHMP assessment procedure.

Additionally, new analysis and associated data submitted during re-examination were not evaluated on the basis of an unadopted procedural advice, and the ad-hoc expert group convened for CINAINU was not provided with essential regulatory documents, including the PIP, PDCO opinion, and key quality dossier elements (eCTD Modules 2.3 & 3). Thus, the Applicant has made the decision to withdraw the application and requests at this point of time from EMA the retraction of CHMP opinion and forthcoming EPAR.

We consent for this letter to be published on EMA website.

Yours sincerely,

[redacted]

Saad Harti, CEO

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10 March 2025

To : EMA Executive Director
CHMP Chair
European Medicines Agency
Domenico Scarlattilaan 6
1083 HS Amsterdam, The Netherlands

cc : CINAINU-4155@ema.europa.e

Ref: CINAINU cutaneous solution – Centralized Marketing Authorization Application
MAA Withdrawal – Follow-Up on Withdrawal Notification & Retraction Request
Submission sequence number: 0012
Reference number: EMEA/H/C/0004155/0000

Dear EMA Executive Director, Dear CHMP Chair,

Legacy Healthcare (France) SAS (the Company) hereby writes to follow up on its letter dated 26 February 2025 (the Withdrawal Letter), notifying the EMA of the withdrawal of the Marketing Authorization Application (MAA) for CINAINU cutaneous solution and requesting the retraction of the Committee for Human Medicinal Products (CHMP) opinion and forthcoming CHMP withdrawal European public assessment report (W-EPAR). Specifically, the Company wants to address the points raised during the post-withdrawal discussions with EMA held on February 28 and March 4, 2025.

The Company reconfirms its consent for the publication of the Withdrawal Letter (attached), which notably outlines the reasons for withdrawal, on the EMA website. Additionally, the Company reaffirms its request for the public retraction of the CHMP opinion and the W-EPAR for Cinainu. This request is justified below.

Justifications for the public retraction request

1. Contradictions between CHMP's grounds for refusal and the EMA-approved Paediatric Investigation Plan (PIP) and the EMA Pediatric Committee (PDCO) opinions: the CHMP's clinical and non-clinical grounds for refusal are in direct contradiction with the EMA-approved PIP for Cinainu and the PDCO's positive opinions about the PIP, PIP modifications, and compliance with the completed PIP.
    - Following the assessment of the data by PDCO (which includes five CHMP members), experts of the EMA Herbal Medicinal Product Committee (HMPC), and the EMA Formulation Working Group (FWG), the PIP was approved by an EMA Decision, explicitly stating that no additional non-clinical studies were required given the absence of anticipated safety concerns regarding the long-term use of Cinainu. Consistent with these evaluations, no safety concerns were identified throughout Cinainu's development. Despite this, on

November 14, 2024, the CHMP adopted a contradictory stance, asserting that the non-clinical data were insufficient and requesting additional non-clinical studies, directly opposing the EMA-approved PIP and the conclusions of other EMA committees.

- The sample size for the single pivotal RAAINBOW Ph 2/3 study in the approved PIP was determined based on a statistical significance threshold of 5% for the primary endpoint, as accepted by the PDCO. However, despite the fact that the study primary endpoint achieved statistical significance (p=0.0488, below the predefined 5% threshold), the CHMP, in its opinion dated November 14, 2024, deemed the level of statistical significance insufficiently strong, thereby contradicting the EMA-approved PIP requirements.
- Similarly, in its opinion dated 26 April 2023, the PDCO formally recognized the Full Analysis Set (FAS) of the pivotal RAAINBOW clinical study as scientifically justified and accepted it as the primary analysis population for demonstrating efficacy. However, in full contradiction, the CHMP, in its opinion dated November 14, 2024, deemed the FAS invalid as a primary analysis population, citing arguments that are not supported by valid scientific, statistical, or regulatory justification - a position the Company fundamentally disagrees with.
- Had EMA Policy No. 009[1] and the CHMP[2] & PDCO[3] rules of procedure been properly followed, these diverging opinions would have been resolved from the outset - within the PIP process - and during the PIP compliance check, ensuring coordinated and consistent guidance and opinions from the EMA committees. Instead, this failure led to misaligned regulatory positions that directly and negatively impact the Company.

2. Failure to consult the HMPC, in violation of procedural rules: despite the CHMP raising quality-related concerns directly linked to Cinainu's herbal substances, the HMPC - EMA's designated expert body on herbal medicinal products - was never consulted during the CHMP assessment procedure. This omission is in direct contradiction with CHMP and HMPC rules of procedure, which explicitly require HMPC consultation in such cases.[4]

Given these serious procedural issues and their negative effects on the Company, Legacy Healthcare has no alternative but to formally request public retraction of the documents related to the CHMP scientific assessment of Cinainu, both those already published and those intended for publication on the EMA website. This retraction should include the reasons for the request and be accompanied by the publication of the Withdrawal Letter along with this follow-up communication. As the Company has emphasized during the post-withdrawal discussions with EMA, the dissemination of these scientifically and procedurally flawed documents is highly prejudicious to Legacy Healthcare. In light of this, the Company urgently requests their immediate retraction to prevent further harm.

Additionally, the Company likes to clarify again that while the issues related to the ad-hoc expert group and the failure to assess submitted data during re-examination were among the Company's reasons for withdrawal, they do not form the grounds for the retraction request, as these issues arose after the currently published CHMP opinion dated November 14, 2024 and the related W-EPAR.

[1] EMEA Policy On Appropriate Coordination Between The Scientific Committees Of The Agency - EMA/124704/2005 Rev.1
[2] Committee for Medicinal Product for Human Use – Rules of Procedure - EMA/270690/2023
[3] Rules of procedure of the Paediatric Committee (PDCO) - EMA/348440/2008 Rev.3
[4] Article 13 of HMPC Rules of procedure - EMA/HMPC/139800/2004 Rev.5

Request for Fee Exemption

Lastly, the Company contests the invoice issued by EMA for the fees related to Cinainu's marketing authorization application. Given that the Company has been granted SME (micro, small, and medium-sized enterprise) status by EMA, and considering that Cinainu followed the scientific advice provided by EMA through the EMA-approved PIP, the fee exemption criterion outlined in Article 6 of Regulation (EC) No 2049/2005 applies.

Furthermore, as the EMA-approved PIP constituted the primary scientific advice for Cinainu's development, which was strictly adhered to by the Company, as evidenced by the PDCO positive opinion on compliance with the PIP, the CHMP's grounds for refusal directly contradict this pre-agreed regulatory framework. Consequently, the fees associated with the examination of Cinainu's marketing authorization application should be waived, given that the regulatory process was seriously compromised by procedural issues and inconsistencies.

Conclusion

The Company consents to the publication of this follow-up letter on the EMA website and looks forward to EMA's response to this urgent matter.

Yours sincerely,

Saad Harti
CEO

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