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Article type : Editorial

EDITORIAL

A novel adaptive design for allergen immunotherapy clinical trials

Short title: Novel study designs for AIT

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the [Version of Record](#). Please cite this article as [doi: 10.1111/ALL.15231](https://doi.org/10.1111/ALL.15231)

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Abbreviations:

AIT, allergen immunotherapy

DBPC, double blind placebo controlled

EMA, European Medicines Agency

EURD, European Union Reference Dates

FDA, US Food and Drug administration

MA, marketing authorization

MS, member states

NPP, named patient product

PSUR, Periodic Safety Update Reports

SME, small and medium enterprises

Key words: *Allergen immunotherapy; regulatory aspects; trial-design; adaptive design; clinical development programs*

Accepted Article

Twenty years have passed from the publication of the Directive 2001/83/EC which, by defining allergen products as medicinal products, lays down the legal and regulatory framework for both diagnostic and therapeutic allergen products to obtain a marketing authorization in EU Countries¹.

However, after 20 years, only a few out of the thousands of allergen products authorised and distributed for allergy diagnostics or allergen immunotherapy (AIT) in EU member states (MS) follow this regulatory background. The main reason for this, stands in the nature of EU Directives that are not mandatory for MS but only request to be followed by a national consistent legislation. Consequently, different interpretations of the Directive generated an extremely heterogeneous situation, despite the several guidelines published by the European Medicines Agency (EMA) on the requirements for marketing authorization (MA) of allergen products ².

In fact, the majority of the authorised allergen products have national MA that are indeed based on limited dossiers. Furthermore, several allergen products are distributed according to Article 5 of the Directive 2001/83/EC as a medicinal products for use by an individual patient (named patient product, NPP), often without an adequate documentation on quality, safety and efficacy³. This heterogeneity makes also difficult an adequate pharmacovigilance through the inclusion of allergen products

in the European Union Reference Dates (EURD) list and the submission of the required Periodic Safety Update Reports (PSUR). Accordingly, actions have been taken and a guidance has been published to harmonize the regulatory requirements for allergen products in EU Countries²⁻⁴. The situation is not better in other parts of the world⁵.

Apart from the uncertainty caused by the heterogeneity of the regulatory approaches to MA of allergen products, the major constraint for allergen manufacturers to embark in a proper MA pathway is represented by time required to reach market access and by the costs, often too high for many small and medium enterprises (SMEs) and for products with a limited economic return. In fact, double blind placebo controlled (DBPC-) trials represent the golden standard to prove efficacy and safety of allergen products and a duration of 3 years of treatment and two years of follow up is requested to claim a sustained effect for AIT products ⁶. In addition, the time required for health technology assessment and its outcome at national (or even regional) level make the process even more risky for companies.

The article of Xinyu Tang and co-workers in this issue ⁷ proposes an interesting three-stage design for AIT trials that prevents from keeping the control arm on placebo for the entire duration of the trial - consequently causing many drop out - while permitting a stagewise statistical evaluation to test for benefit at the end of each stage. The authors propose a three stage design in which the placebo group in Stage 1 crosses over to receive active treatment in Stage 2. In Stage 3, AIT is discontinued to determine whether benefit is maintained posttreatment. Inferential statistics is applied to support the three-stage design for clinical trials to determine clinical efficacy, treatment response over time, and sustained response to AIT.

This adaptive approach may allow a more rapid marketing authorization with a short-term indication after Stage I, to be extended if Stage II and III show positive long-term effects. This approach might be extremely attractive for companies that are reluctant to embark on long-term AIT clinical trials, for paediatric studies in which long-term use of placebo is a matter of ethical concern and for all allergic patients who might have a more timely access to safe and effective products.

The authors make clear in the disclaimer that the opinions expressed in the article represent their personal point-of-view and do not necessarily reflect the views and policies of the institution they belong to, the US Food and Drug administration (FDA).

However, should the design proposed represent a more general attitude of regulatory bodies to be open to novel adaptive designs, this would make easier the MA of safe and effective diagnostic and therapeutic allergen products.

AIT remains as the only disease modifying treatment option, with increasing body of evidence on its efficacy and safety⁸. A close collaboration among authorities, industry, researchers and clinicians is needed to pave the way to realistic, harmonized and feasible MA pathways to validated allergy diagnostics and to well-documented AIT products for a worldwide early access of allergic patients.

Disclosure of conflicts-of-interest: Dr. Bonini has no Col to disclose. Dr. Pfaar Dr. Pfaar reports grants and personal fees from ALK-Abelló, grants and personal fees from Allergopharma, grants and personal fees from Stallergenes Greer, grants and personal fees from HAL Allergy Holding B.V./HAL Allergie GmbH, grants and personal fees from Bencard Allergie GmbH/Allergy Therapeutics, grants and personal fees from Lofarma, grants from Biomay, grants from Circassia, grants and personal fees from ASIT Biotech Tools S.A., grants and personal fees from Laboratorios LETI/LETI Pharma, personal fees from MEDA Pharma/MYLAN, grants and personal fees from Anergis S.A., personal fees from Mobile Chamber Experts (a GA2LEN Partner), personal fees from Indoor Biotechnologies, grants and personal fees from GlaxoSmithKline, personal fees from Astellas Pharma Global, personal fees from EUFOREA, personal fees from ROXALL Medizin, personal fees from Novartis, personal fees from Sanofi-Aventis and Sanofi-Genzyme, personal fees from Med Update Europe GmbH, personal fees from streamedup! GmbH, grants from Pohl-Boskamp, grants from Immunotek S.L., personal fees from John Wiley and Sons, AS, personal fees from Paul-Martini-Stiftung (PMS), personal fees from Regeneron Pharmaceuticals Inc., personal fees from RG Aerztefortbildung, personal fees from Institut für Disease Management, personal fees from Springer GmbH, personal fees from AstraZeneca, personal fees from IQVIA Commercial, personal fees from Ingress Health, outside the submitted work.

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