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Rheumatology and Immunology Working Party (RIWP)

Concept paper on the new reflection paper on the clinical investigation of medicinal products for the treatment of Systemic Sclerosis

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1. Introduction

The European Alliance of Associations for Rheumatology (EULAR) has recently published updated recommendations for the treatment of systemic sclerosis (SSc) (Del Galdo et al, 2025[1]). This publication puts forward that *"SSc is a rare connective tissue disorder characterised by the association of autoimmune features with vascular manifestations and culminating in tissue and vascular fibrosis of the skin and internal organs, with highly variable outcomes. Type and severity of organ involvement drive the heterogeneous prognosis, but overall SSc remains the rheumatic disease with the highest morbidity and mortality, despite recent improvement in survival"*. The publication also stresses that the high heterogeneity in the presence and severity of skin and visceral involvement is a major challenge in trial design (Del Galdo et al, 2025[1], Del Galdo et al, 2020[2]).

There is currently no scientific guidance from the European Medicines Agency (EMA) on the clinical investigation of medicinal products for the treatment of SSc. This is needed to guide development and support marketing authorisation applications for this condition.

2. Problem statement

SSc, also known as scleroderma, is a rare condition with a high unmet need for effective treatments, due to its high morbidity and mortality, limited efficacy and tolerability of current therapies, and potentially rapid disease progression. Currently, centrally approved products in the EU are for SSc-associated disease manifestations only, i.e. a) interstitial lung disease (SSc-ILD), b) digital ulcers (reduction of new and ongoing digital ulcers), and c) pulmonary arterial hypertension (PAH) secondary to scleroderma without significant interstitial pulmonary disease. There are however, at present, no products specifically approved for a general SSc indication.

Guidance on how to design development programmes to support authorisation of medicinal products for both specific features of SSc as well as products aimed at a general SSc indication is needed, also taking into account the regulatory experience with applications for scientific advice and for marketing authorisation. Important aspects include overall study design elements and endpoints selection.

3. Discussion (on the problem statement)

The following issues, related to the design of development programmes for the treatment of specific features of SSc and products aiming for a general SSc indication, will be addressed in the new reflection paper:

- Number and type of studies recommended, also considering the rarity of the condition. In a recent systemic review and meta-analysis on the incidence and prevalence of SSc across the world, overall pooled prevalence of SSc was 17.6 (95% confidence interval (CI) 15.1, 20.5) per 100,000 while the prevalence in the Europe was 14.8 (95% CI 11.6, 18.8) per 100,000 (Bairkdar et al, 2021[3]).
- Overall design and duration of exploratory and confirmatory studies recommended. This will include the design to support short-term and long-term treatment (demonstration of maintenance of efficacy needed).
- Study population in relation to target indication and treatment goals. This will include classification criteria for SSc, criteria related to different disease manifestations, disease subsets (limited cutaneous/diffuse cutaneous, division of patient subgroups based on specific antibodies), and stage of the disease. The staging into early or late disease can be aided by nailfold capillaroscopy. As acknowledged, the high heterogeneity of this disorder is a challenge in clinical trial design (Del

Galdo et al, 2025[1], Del Galdo et al, 2020[2]). Paediatric development for this indication is generally foreseen and some considerations for paediatric development may also be included in the reflection paper. These considerations should be agreed with the Paediatric Committee (PDCO).

- Standard of care for interventional studies, considering recommendations for allowed (versus prohibited) concomitant treatment and rescue treatment. Recent developments and regulatory approvals need to be reflected.
- Stratification factors, especially with regard to the different disease subsets (see above).
- Assessment of efficacy:
  - Goals for therapy could concern either efficacy on the overall disease course or on a specific disease manifestation (for example (e.g.) SSc-ILD or cutaneous disease) for a specific disease subtype or all subtypes. Treatment targets may include delay of onset or prevention of progression of clinical manifestations (e.g. internal organ involvement). Disease modification may be included as a treatment goal if a clear definition of this term is considered feasible and possible to link to an appropriate outcome measure.
  - Selection of (co-)primary, secondary, and exploratory endpoints, based on the target indication/goals of therapy and taking into consideration the heterogeneity of the disease manifestations. The heterogeneity includes internal organ involvement, and the variety of potential internal organs involved. Whether potential endpoints are well-established, sufficiently validated, and fit for purpose will need to be considered.
  - Potential endpoints are:
    - Dedicated composite endpoints for subgroups or for the overall SSc population.
    - Patient Reported Outcomes (PROs) including PROs dedicated for SSc and/or different SSc manifestations.
    - Endpoints/measures related to specific disease manifestations such as forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) for SSc-ILD, 6 Minute Walk Test and / or right catheterisation for e.g. PAH, Modified Rodnan Skin Score (mRSS) for skin manifestations (fibrosis), and number of (new) digital ulcers. For some endpoints, a cross-reference to other EMA guidance documents may be appropriate.
    - Endpoints to measure an effect on specific manifestations not mentioned above e.g. gastrointestinal manifestations, musculoskeletal manifestations including arthritis, myopathy, and contractures, renal crisis, Raynaud's phenomenon, and calcinosis cutis.
    - Assessment of effects on survival acknowledging the challenges associated with these evaluations in a rare disease.
  - Statistical considerations and potential estimand and estimand strategies, taking into account ICH E9(R1) addendum on estimands and sensitivity analysis.
- Assessment of safety:
  - Size of safety database; number of exposed subjects and duration of exposure. It needs to be considered that SSc is a chronic condition, requiring long-term treatment.
  - Extent of support from safety data that can be derived from other, related conditions. Medicinal products with immune suppression as mechanism of action are often assessed across various rheumatological or systemic auto-immune conditions and safety may, to some extent, be

possible to extrapolate across diseases. For such extrapolation exercises, similarity between the conditions in terms of comorbidities, comedication, and other factors influencing the risk for adverse reactions of medicinal products are of primary relevance.

- Data may be generated in post-approval setting; this could apply for data on long-term effects and rare events.

4. Recommendation

The Rheumatology/Immunology Working Party (RIWP) of the Committee for Human Medicinal Products (CHMP) recommends drafting a new guidance on the clinical investigation of medicinal products for the treatment of SSc taking into account the issues listed in section 3.

A reflection paper is considered the most appropriate form of guidance at this stage of knowledge and regulatory experience.

5. Proposed timetable

Release for consultation on 30 June 2025, deadline for comments 30 September 2025.

6. Resource requirements for preparation

The drafting of the new reflection paper will involve representatives of the RIWP, including one Rapporteur. It is anticipated that at least one plenary session discussions at the RIWP will be needed.

7. Impact assessment (anticipated)

It is anticipated that the new reflection paper will have an impact on the clinical development of medicinal products for the treatment of SSc. The aim is to consolidate the current regulatory view on the design of the clinical development programmes of medicinal products in this condition, and to be helpful to achieve consensus in the evaluation of such products by regulatory authorities.

8. Interested parties

Pharmaceutical Industry, Academia, European Union Competent Authorities and patients and health care professional groups. Consultation with other working parties or committees will be initiated, as appropriate.

9. References to literature, guidelines, etc.

1. Del Galdo, Francesco, Alain Lescoat, Philip G. Conaghan, Eugenia Bertoldo, Jelena Čolić, Tânia Santiago, Yossra A. Suliman et al. "EULAR recommendations for the treatment of systemic sclerosis: 2023 update." *Annals of the rheumatic diseases* 84, no. 1 (2025): 29-40.
2. Del Galdo, Francesco, Collette Hartley, and Yannick Allanore. "Randomised controlled trials in systemic sclerosis: patient selection and endpoints for next generation trials." *The Lancet Rheumatology* 2, no. 3 (2020): e173-e184.
3. Bairkdar, Majd, Marios Rossides, Helga Westerlind, Roger Hesselstrand, Elizabeth V. Arkema, and Marie Holmqvist. "Incidence and prevalence of systemic sclerosis globally: a

comprehensive systematic review and meta-analysis." *Rheumatology* 60, no. 7 (2021): 3121-3133.