Immunology &
Dermatology Franchise
Novartis Pharma

IMI Topic 3: Development of sensitive and validated clinical endpoints in primary Sjögren's Syndrome (pSS)

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March 27, 2017

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Unmet need in pSS

- Primary Sjögren's syndrome (pSS) is a common systemic autoimmune disease affecting as a hallmark exocrine glands leading to sicca symptoms of the eyes and the mouth
- Systemic and extra-glandular manifestations can often develop as well. A negative impact on quality of life (QOL) is prominent, mainly due to the disabling fatigue as the most important factor in loss of work productivity
- Moreover, pSS patients have 9-fold higher risk of developing B cell lymphomas
- Only symptomatic treatments are available for commercial use. Given the significant heterogeneity in the clinical presentation and course of patients with pSS, success in therapeutic trials will depend on a better understanding of disease phenotypes to drive patient selection and stratification
- There are no treatments for systemic correlates of the disease and there have been no industry sponsored studies that have been able to show a disease modifying effect

References:

1.Rischmueller M, Tieu J, Lester S. Primary Sjögren's syndrome. Best Pract Res Clin Rheumatol. 2016;30:189-220.

2. Meijer JM, Meiners PM, Huddleston Slater JJ, Spijkervet FK, Kallenberg CG, Vissink A, Bootsma H: Health-related quality of life, employment and disability in patients with Sjogren's syndrome. Rheumatology. 2009;48:1077-82.

The Challenge

- Currently, published data from placebo-controlled and adequately powered clinical trials in pSS are scarce [3].
- Although specific novel, validated treatment outcome measures have been developed recently, e.g. European League against Rheumatism (EULAR) Sjögren's syndrome disease activity index (ESSDAI) and EULAR Sjögren's syndrome patient reported index (ESSPRI – 3 Qu), their recent use in clinical trials has yielded mixed results.
- Important features of pSS such as swallowing difficulties, dietary problems, mental health challenges, sexual dysfunction, dental problems (including tooth loss and decay) are not (adequately) captured.
- Overall, the utility of the currently available measures (including sensitivity to change in Patient Reported Outcomes (PROs) and in various ESSDAI domains) in assessing efficacy and disease-modifying potential of an investigational drug is still to be determined
- Moreover, no objective validated measure or functional marker of disease activity for assessing therapeutic benefits of improvement is currently available.

In conclusion: sensitive and validated endpoints including objective measures/biomarkers of improvement are needed to increase the likelihood of success of drug development in pSS.

Ref: see back-up

Scope: Develop sensitive and validated clinical endpoints for use in future clinical trials of pSS

- Identification, development and validation of pSS-related outcome measures including clinical, PRO, laboratory, bio-behavioural activity and imaging parameters (biomarkers), applying the following step-wise approach:
  - Data generation and review
  - Development of new outcome measures
  - Application and validation by prospectively testing of these measures
  - Analysis of the outcome
- It is anticipated that the scoring system(s) will require a combination of objective and subjective outcome measures to improve upon existing scoring systems (e.g., selected, core set of ESSDAI domains combined with ESSPRI fatigue or other key PRO items).

Expected Key Deliverables

- (i) Identification and characterization, (ii) prospective qualification and (iii) regulatory acceptance of **disease scoring tools to assess key features of pSS** (disease activity, organ spec. improvement, …)
- Identification and validation of a **biomarker** or sets of prognostic markers that could be used as a surrogate endpoint(s) in Phase II trials
- Development of an endpoint model to determine what the **patient- (and payer-) relevant endpoint measures** are, independent of where treatments have an effect. → To be used to develop a relevant PRO measure that can be deployed in future clinical trials.
- Development of a suitable methodology to capture **semi-continuous bio-behavioural activity data in pSS patients** by exploring activity patterns and features which are specific to pSS fatigue symptomatology.
- **Patient phenotyping to characterize different subgroups of pSS** . For this, clinical data as well as established and novel biomarker data will be used that could identify commonalities and differences across subgroups as well as response to therapies.

In-Kind contribution from the industry consortium

- Program management
- Clinical trial design (e.g. adaptive design, modelling/simulation…)
- Clinician, clinical pharmacologist, statistician or clinical scientist from each company to act as a company network champion
- Clinicians for communication, on-site visits, and other interactions with academic medical centres, investigators, and advisory boards
- Biostatistical/ data management expertise
- Regulatory expertise in interacting with EMA and other authorities
- Clinical operations
- Business planning and development; contractual agreements, legal councelling
- Industry-sponsored clinical trials and the data generated from such clinical trials to test the viability of the network.

Expected expertise from the applicant consortium

- Experience and know-how in conducting clinical trials in Sjogren's
- Expertise in drug development (e.g. Clin. Pharm., study design and conduct)
- Access to a large representative pSS population(s)
- Expertise in patient reported outcomes, development and validation
- Physicians/HCPs covering the spectrum of clinical manifestations of pSS (rheumatologists, dental care etc);
- Patient advocacy organisations (actively contributing to development of study design, feasibility assessment, clinical endpoints, and risk-benefit)
- Expertise in developing regulatory guidelines and in interacting with EMA or national regulatory authorities, but also national payers
- Information technology/ data management
- Expertise in legal and clinical compliance aspects (ICH, GCP)
- Strong project management and communication expertise
- Office administration and website management

Overall framework

- **EFPIA members**
  - Novartis (lead), GSK, BMS, Servier, Lilly

- **Duration**
  - 72 months

- **Indicative budget**
- 8 mio Euro funding
- 8 mio Euro in-kind contribution