APDS Registry
an ESID Registry level 3 project

NEWSLETTER No. 1
June 2017

APDS Registry: Prospective observational study on natural history, treatment and outcome of patients with APDS

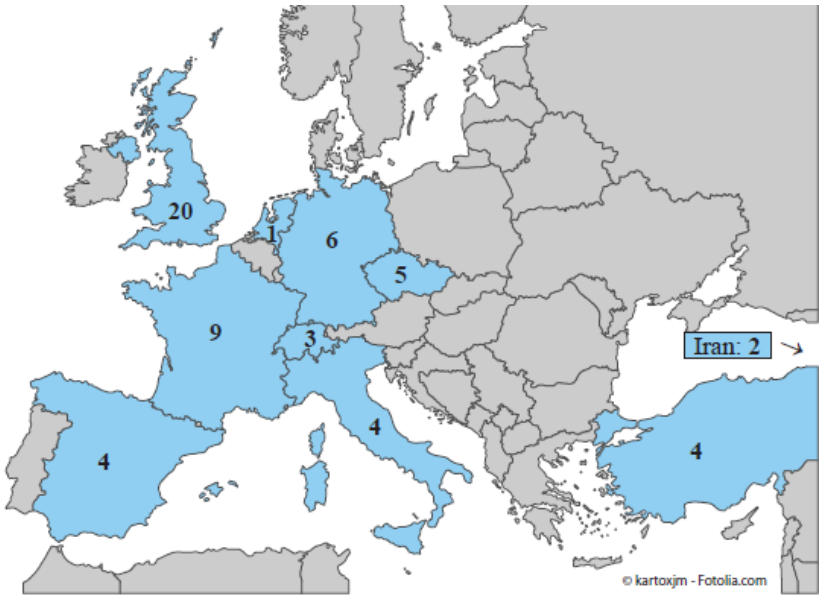
Dear ESID investigators,

The APDS Registry is an ESID Registry level 3 project and was initiated to better define the natural history of patients with the combined immunodeficiency Activated PI3-Kinase Delta Syndrome (APDS). The aim is to document the disease evolution and the impact of different treatment strategies, in order to identify predictors of outcome. The registry is supported by Novartis, GSK and UCB and may also be used to offer patients participation in clinical trials with selective p110δ inhibitors.

In this first Newsletter we would like to give you an overview about the project and associated activities.

Current status of recruiting sites and registered patients

We express our thanks to the teams of 20 study sites, which have already included 57 patients. The first longitudinal data are now available from 19 patients.



Description of cohort

Patients with genetically confirmed APDS are registered with a retrospective case report form, followed by prospective 6-monthly follow-ups, allowing longitudinal clinical and biological assessment. Here the current basic parameters of the 57 patients registered by June 2017:

age range:	2 to 48 (median: 17 years)
gender distribution:	28 female, 29 male
genetic classification:	37 APDS1, 20 APDS2

A first detailed report with a focus on autoimmune manifestations will be prepared for the ESID 2017 meeting (http://esid2017.kenes.com/).

Project funding

The APDS Registry is funded by industry partners. This allows financing development and maintenance of the ESID Registry-based online documentation section for APDS patients as well as project management including ethics, data management and quality controls. Importantly, the financial support also allows reimbursement of documentation activities for the participating centers (case fees).

Based on informed patient consent, anonymized data from the APDS Registry are available to industry partners for their purposes (e.g. designing a drug trial or include results in regulatory approvals). This also means that industry partners can approach centers contributing to this project (via the study coordination office) to offer treating physicians to inform their patients about participation in a pharmaceutical study.

The ESID documenting centers remain in full possession of the registry data and ESID investigators have the right to publish data extracted from the APDS Registry at any time – with prior information of the industry partners. Data access and publication rules for this and all other ESID Registry projects have been specified and approved by the ESID board.

Clinical trials by industry partners

GlaxoSmithKline (GSK)

GSK2269557: A targeted inhaled treatment with low systemic exposure, which will directly inhibit PI3Kδ function and thereby reduce the burden of recurrent pulmonary, ear, and sinus infections and associated morbidity in patients with activated PI3Kδ.

GSK2269557 is a highly potent and selective PI3Kδ inhibitor, delivered once daily by the inhaled route. It has been shown to be safe in healthy subjects, subjects with Chronic Obstructive Pulmonary Disease (COPD), and subjects with uncontrolled asthma. Our ongoing study in patients with APDS/PASLI is an open-label study to investigate repeat doses of GSK2269557, administered at a dose of 700 micrograms, for up to 84 days in addition to current standard of care (ClinicalTrials.gov number: NCT02593539). Eligible subjects will be aged 18 or older with a clinical phenotype consistent with APDS, including a history of recurrent ear, sinus or pulmonary infections, and with a known type I or type II APDS-associated genetic PI3K delta mutation. The primary endpoints will be safety and PK but we will also measure a number of relevant biomarkers to explore the impact of GSK2269557 on disease biology and increase disease understanding. These data will complement our program of basic research into APDS, being carried out in collaboration with Professor Alison Condliffe (University of Sheffield, UK), Dr Klaus Okkenhaug (Babraham Institute, UK) and Dr Anita Chandra (Babraham Institute & Addenbrookes NHS Trust, UK) under an MRC MICA grant (MR/M012328/1, 2015-2020).

Novartis

Novartis has conducted an open-label, non-randomized, within-subject dose-finding study on escalating doses of the potent and selective PI3Kδ inhibitor Leniolisib (CDZ173) over 12 weeks in six patients with APDS (ClinicalTrials.gov number, NCT02435173). Leniolisib led to marked improvements in the clinical presentation of patients. Lymphoproliferation was strongly reduced as MRI/CT scans at the end of treatment showed regression of lymph nodes and spleen size by 40%. Treatment led to a normalization of naive B cell numbers, a reduction in the number of previously elevated transitional B cells and in PD-1+CD4+ T cells and senescent CD57+CD8+ T cells. In parallel, an exposure-dependent reduction of PI3K/AKT pathway activity was detected ex vivo.

Patients reported increased energy levels and/or decreased fatigue. No treatment-induced relevant clinical or laboratory abnormalities or adverse events limiting their physical activity or wellbeing were observed. Participating patients are offered continued Leniolisib treatment in an extension study. Leniolisib is currently studied in patients with primary Sjögren's syndrome (ClinicalTrials.gov number: NCT02775916).

UCB

Seletalisib is a potent, selective PI3Kδ inhibitor directly targeting the causal mechanism in APDS. Phase 1 clinical studies with Seletalisib demonstrated a manageable safety and tolerability profile, displayed PK results supportive of once-daily dosing and evidence of biological effect. In ex vivo studies using T cell blasts derived from both APDS1 and 2 patients, Seletalisib inhibited PI3K signalling supporting a proof of-concept study in APDS. This study is ongoing, actively accepting participants and aims to assess the safety, tolerability, PK and preliminary efficacy of Seletalisib in APDS patients by exploring the effect of dosing on clinical and cellular endpoints. Results are expected in 2017 Q3.

How can you include a patient?

It would be great if you could contribute to this initiative with data from your patients. To notify a new patient, you can just fill in and send a 1-page fax form available at: https://esid.org/Working-Parties/Registry/Studies/APDS-Registry.

If you want to have access to all study documents and benefit from the financial reward for data entry, please formally register your center for the APDS Registry and ask for username and password: annette.uhlmann@uniklinik-freiburg.de

All essential study documents are then available for download at:
https://www.uniklinik-freiburg.de/cci/studien/apds-registry.html?L=0BreisacherSchriftf

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