ATAXIA ADVISORY COMMITTEE FOR THERAPEUTICS:

TERMS OF REFERENCE

Contact:

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https://ataxia-global-initiative.net/ataxia-act/

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OVERVIEW

Ataxia Advisory Committee for Therapeutics (Ataxia ACT) is one of the trial readiness services of the Ataxia Global Initiative (AGI). It aims to optimize the planning and execution of preclinical and clinical drug development programs for (all forms of) ataxias. Ataxia ACT provides confidential, unbiased, multi-stakeholder and multidisciplinary expert advice to optimize therapy development, by either a) steering studies along a realistic and well-informed plan to clinical trial/later phase clinical activity or b) encouraging a change of direction or approach, to avoid failure further down the line. It is based on the blueprint of the successful Treat-NMD TACT.

MAIN AIM: REVIEW AND PROVIDE OBJECTIVE ADVICE ON THE TRANSLATION AND DEVELOPMENT PATHWAY OF THERAPEUTIC PROGRAMS IN ATAXIAS.

Ataxia ACT **can address:**

- Trial design
- Drug formulation
- Bioavailability and toxicology
- Regulatory considerations
- Recommendations including go-no-go milestones

REMIT OF THE COMMITTEE

The Ataxia ACT review process is thorough, multidisciplinary and educational. It is aimed at helping researchers and drug developers navigate the full research and development process. Ataxia ACT recommendations aim to facilitate human proof of concept (POC) trials, by generating preclinical and clinical data that will enable subsequent development decisions and potential registration.

Through its comprehensive quality recommendations, Ataxia ACT may act as an important diligence body and help stimulate funding opportunities. While the Ataxia ACT process is independent of any funding stream, applicants can use its reports to support funding applications. An Ataxia ACT review is NOT an endorsement by Ataxia ACT or Ataxia Global Initiative that a drug has any particular status in terms of regulatory or funding potential.

COMPOSITION OF THE COMMITTEE

The committee is a group run under the aegis of the AGI. However, membership of the committee is not limited to AGI members and partners but rather is selected by the Ataxia ACT chairs together with the Ataxia ACT office from the pool of experts nominated to

represent the very best expertise available to address the issues pertinent to the Ataxia ACT remit. The core committee covers a wide range of the expertise described below. The core committee has responsibility for taking decisions about the running of ACT, strategy and direction along with the office under the guidance of the chair. Core committee members are invited to attend all ACT meetings and convene together in advance of the wider group. Membership of the core is for 3 years after which a replacement will be sought to cover a similar area of expertise. When members leave the core committee they re-join the extended committee. The two chairs of the committee are appointed by the ACT core committee and serve for three years.

Additional experts are co-opted to an extended committee for assessment of areas not within the immediate expertise of the core committee.

The AGI office, located in Tübingen, Germany, provides administrative support for the Ataxia ACT extended and core committees. AGI office members assisting the committees are referred to as the Ataxia ACT office.

All committee members undertaking reviews and attending face-to-face meetings are reimbursed for reasonable, standard class travel expenses and are eligible to receive an honorarium for each meeting attended, with the exception of government employees acting in official capacity. All committee members sign a confidential disclosure agreement and complete a declaration of all potential conflicts of interest. Committee members are requested to update their conflict of interests before each review meeting. A short member's biography is published on the AGI website.

OBSERVERS

In order to introduce new potential reviewers, educate patient organisations or other key stakeholders about the ACT process, observer status may be granted for review meetings. This allows individuals who have not been part of an ACT review previously to attend and observe a meeting under full CDA and CoI agreements. Observers do not take part in the review but may view the applications and be present during discussions. They do not contribute to the advice and report given to applicants. Funders of meetings do not necessarily receive observer status and individuals should only observe once. The applicants will be informed about observation requests to the office.

APPLICATION PROCESS TO ATAXIA ACT

Suggestions for programs that could benefit from an Ataxia ACT review are solicited from the ataxia community. Applicants can include principal investigators planning a study, preclinical investigators who wish to move to the clinical arena, industry sponsors or funding bodies seeking input on the feasibility of a given program considered for funding. All applicants are expected to complete a standard application and provide supporting data. The completion of this focused application form is in itself an educational tool. Ataxia ACT proactively calls for nomination of drugs and approaches potential principal investigators to inform them on the role of ACT. All core and extended members of Ataxia ACT as well as the office, applicants, reviewers and observers are required to sign a confidentiality agreement.

COSTS FOR APPLICANTS

While the Ataxia ACT operates on a not-for-profit basis, to sustain its activities, it relies on application fees to cover the incurred expenses (15.000-40.000 €). The fee depends on two factors: the company's size and the incurred expenses for the actual meeting. The applicants will receive the invoice after their pre-application has been accepted.

ROLES WITHIN THE COMMITTEE

CORE COMMITTEE

Chairs: The two chairs will work with the Ataxia ACT office on the following tasks:

- Review pre-applications for suitability to be reviewed by the ACT;
- Chair the meeting (together with the lead reviewers);
- Oversee the preparation of the report and recommendations.

Patient (organisation) representation: to provide the patient perspective on the proposed studies.

Preclinical experts: to appraise critically the preclinical data either published or unpublished on the drug under study against the defined standards for preclinical assessments of animal models. Confidentiality agreements protect unpublished data.

Toxicology experts: to advise on the current status of human exposure to the drug in question including, if relevant, paediatric data.

Pharmacology experts: to advise on the current status of pharmacokinetic and pharmacodynamic data available for the product and to make recommendations for studies needed for regulatory approval.

Regulatory experts: to advise on the likelihood of regulatory approval for entering the clinic (and potentially subsequent registration) including acceptability of endpoints. Expertise covers both Europe and USA.

Clinical trial expert representation: to advise on the protocols likely to be necessary to test the drugs in the clinic, patient numbers and likely numbers of trial sites and potential sample costings.

Clinical representatives: clinic leaders from different geographical areas representing major clinical networks (e.g. Europe and USA). To advise on the practicalities of recruitment to a particular protocol in the context of other competing demands on clinic time and commitment and other general protocol issues.

Statistic expert: to advice on statistical accuracy of trial design.

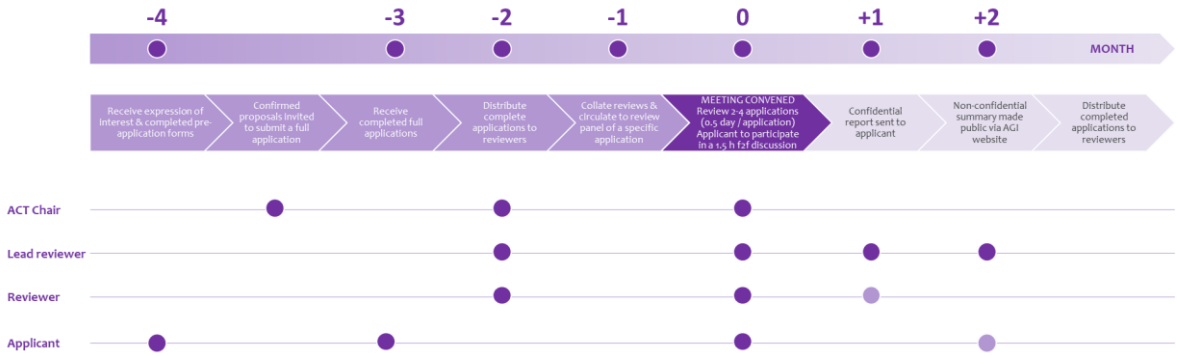
EXTENDED COMMITTEE

In addition to the Core Committee who attend all review meetings, Ataxia ACT has a pool of global experts who are referred to as our extended committee. For each Ataxia ACT application, a bespoke panel is put together with invited reviewers selected from the extended committee who are best placed to answer specific questions of the applicants and provide tailored multidisciplinary advice.

OFFICE

Ataxia ACT office is responsible for all logistical aspects of planning, conducting and follow up from review meetings. The office also helps identify additional expertise or individuals that could contribute to the ACT reviews.

PROCESS AND TIMING



The figure shows the different steps of an ACT review and the timeline. The dots in the lower part show where each player (ACT chairs, (lead) reviewer, applicant) is involved.

PRE-APPLICATION

Potential applicants complete a pre-application following expression of interest for an ACT review. Pre-applications are reviewed by the chair and office to assess their suitability for a full review.

FULL APPLICATION

Full applications are completed approximately 3 months prior to the review meeting. Completing the application focuses the applicant on a number of important considerations including: scientific rationale, the appropriateness and interpretation of the preclinical studies performed, safety and toxicology issues, drug distribution and kinetics, feasibility and cost of drug manufacturing and supply, context of the project in the clinical development plan and regulatory consideration critical to advancing a compound into the clinic. A lead reviewer and additional multidisciplinary reviewers are selected for their specific expertise as it relates to each application. These reviews are distributed to the full core committee and all reviewers prior to the meeting.

MEETINGS

Meetings are scheduled twice a year – generally one in Europe and one in the US, to review two to four applications. A half day is devoted to discussion for each application including a session with the applicant to provide clarifications as needed and ensure the subsequent committee report is as relevant as possible.

Please see our website for the currently scheduled meetings:

https://ataxia-global-initiative.net/ataxia-act/

REPORT

The report is generated by the lead reviewer and approved by the review panel. It will be sent by the office to the applicant within 6 weeks of the meeting. The report includes an objective assessment of the project plan and recommendations for the program. Typically, the applicant poses important questions in writing to the Ataxia ACT, and these are addressed in the written review. The applicant receives this full report and then a non-confidential summary of the report (which is agreed with the applicant) is detailed on the Ataxia ACT website.