ATAXIA GLOBAL INITIATIVE
worldwide platform for clinical research in ataxias

ATAXIA ADVISORY COMMITTEE FOR THERAPEUTICS:

TERMS OF REFERENCE

OVERVIEW

One of the trial readiness services of the Ataxia Global Initiative (AGI) is to create an Ataxia Advisory Committee for Therapeutics (ACT) to optimise the planning and execution of early stage and later phase clinical research on (all forms of) ataxias.

The main objective of the Ataxia ACT would be to provide a valuable resource and service to the ataxia community by giving 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.

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

CONTEXT

The Ataxia ACT is a blueprint of TREAT-NMD Advisory Committee for Therapeutics (TACT). Established in 2009, TACT is a unique multi-disciplinary international group of basic scientists, healthcare professionals, patient advocacy representatives, regulatory experts and industry drug development experts, who meet twice a year to review and give objective advice on the development pathway of therapeutic programs in rare neuromuscular diseases. It aims to help the applicant to position the candidate compound along a realistic and well-informed pathway to clinical trial and eventual registration, by identifying potential pitfalls in clinical trial design and giving independent and transparent advice.

TACT has proven to be a key resource in the quest to optimise the planning and execution of early stage and later phase clinical research in this community. 56 applications have been reviewed until 2019. Although originally developed for the neuromuscular field, the model itself is readily transferable to many other rare disease areas as they share similar challenges, including: low patient numbers, lack of clarity around outcome measures, lengthy trials, poor pre-clinical data, lack of natural history data.

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.

COMPOSITION OF THE COMMITTEE

The committee is a group run under the aegis of AGI. However, membership of the committee is not limited to AGI members and partners but rather is selected by the 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 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.

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 ACT as well as the office, applicants, reviewers and observers are required to sign a confidentiality agreement.

ROLES WITHIN THE 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.

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.

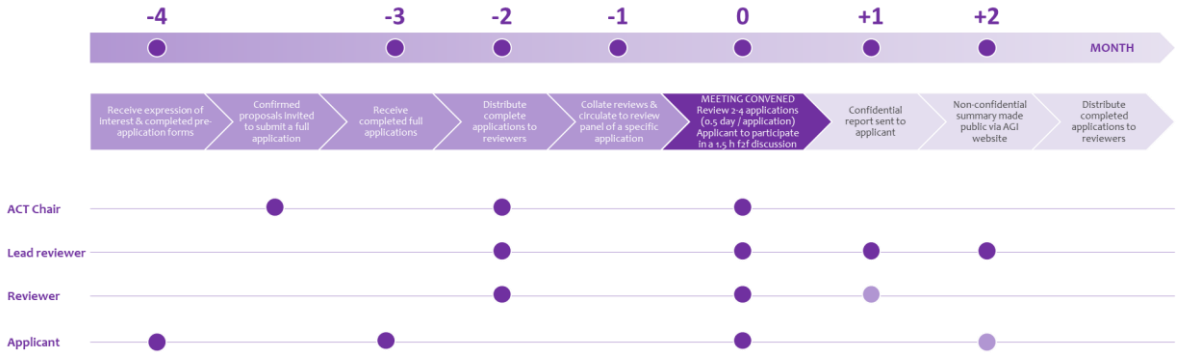
Ethical input: to advise on the ethical dimensions of the proposed studies.

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

Ataxia ACT office: supports 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.

Relationships with funders: funders can enter into a contract with Ataxia ACT to perform work in partnership or on their behalf. Funding an ACT meeting does not imply that funders will be granted attendance to the meeting.

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. Patient representatives also complete written reviews, according to standardized forms, in advance of the meeting. 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.

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.