Regulatory workshop in Neuromyelitis Optica (NMO) and Spectrum Disorders: Clinical trial designs

Session 3: Endpoints Industry

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Challenge

- Primary endpoint must provide data to meet the evidentiary standard for approval
- Primary endpoint must be chosen that can demonstrate substantial evidence of effectiveness/clinical benefit in patient population

EU Regulatory Framework for Choosing of Endpoints in NMO

1. Study Design Perspective:

   CHMP *Guideline on Clinical Trials in Small Populations* (CHMP/EWP83561/2005)

2. Disease Perspective:

   CHMP *Guideline on Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (EMA/CHMP/771815/2011,Rev 2)

Regulatory Framework (1)

CHMP Guideline on Clinical Trials in Small Populations (CHMP/EWP83561/2005)

- No methods exists that are not applicable to larger populations
  - Quality randomised controlled trials are appropriate
  - Any deviations should be prospectively considered
- However, EMA acknowledges the challenges of small populations and (in our interpretation) adopts a pragmatic view in the Guidance of what is acceptable in terms of choice of primary endpoint

Regulatory Framework (2)

- Choice of Primary Endpoint –addressed in the EMA Guidance
  - Clinically relevant, measurable and interpretable endpoint need to be used
  - Guidance provides examples of grades of acceptable endpoints
    - ‘Hard’ endpoint - E.g. Cure of disease, Overall survival
    - Time to Event Endpoints - E.g. time to survival or disease progression guideline classes as “intermediate”
    - Relief of symptoms may be an acceptable endpoint even in the absence of demonstration of benefit on disease progression or survival

Regulatory Framework – Disease Area Guidelines (1)

- No guideline for NMO but guideline exists for the related and more common demyelinating disease **Multiple Sclerosis:** Draft Guideline on *The Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis* (EMA/CHMP/771815/2011,Rev 2) which could be considered a reference point
- Primary Efficacy Parameters: Distinctions made between SPMS, PPMS and RRMS
  - SPMS and PPMS: Clinically measured prevention or delay of disability progression
  - RRMS: Relapse Rate (ARR), although not accepted as surrogate for disease progression, hence progression of disability should be evaluated
  - EDSS accepted as standard for measuring disability progression
- For recent therapies, most primary outcome measure has been ARR and some element of worsening disability as measured by change in EDSS

Regulatory Framework – Disease Area Guidelines (2)

- Other disease guidelines may be more relevant to NMO:
- EMA *Guideline on clinical evaluation for stroke and systemic embolic events (SSEs) in patients with non-valvular atrial fibrillation* (EMA/CHMP/450916/2012) proposes composite 1° endpoint of time to 1st stroke and number of SSEs.
  - Stroke could be viewed as more similar to NMO than MS because of permanent damage at each event (though SSEs not relevant here)

Candidate Primary Endpoint(s) for NMO

- Progression in disability as assessed by Annualised Relapse Rate (ARR)
- Progression in disability as assessed by Time to First Relapse (TFR)
- Surrogate Endpoints. Candidates proposed but none validated for NMO
  - Serum Anti-Aquaporin-4 antibody levels?
  - MRI? (used in early phase MS studies as sign of therapeutic potential)

TFR vs. AAR

Comparison of TFR vs. AAR made from 3 perspectives:

1. Ethics and patient/clinician acceptance of study
2. Duration of double-blind period
3. Study statistics

TFR vs. ARR: Ethics and Patient/Clinician Acceptance of Study

TFR	ARR
PROS: • Avoids ethical issue of keeping patients on same trial treatment after 1st relapse • Each relapse in NMO has permanent and major consequences in terms of disability • Once relapse occurs, alternative treatment should be given (effective, unlicensed alternatives are available) - TFR endpoint allows this • Makes trial participation more attractive to patients and clinicians **CONS:** ---	**PROS:** --- **CONS:** • Clinical experts have advised that ARR not an acceptable endpoint for a placebo-controlled NMO trials because neurological effects of relapse are permanent thus pts need to be offered alternative treatment at 1st relapse on trial • Even if ARR were 1° endpoint, relapsers are likely to be withdrawn from trial for alternative treatment therefore duration of placebo-controlled efficacy and safety data would be capped • No approved active controls are available in this indication

TFR vs. ARR: Duration of Double-Blind Study Period

TFR	ARR
PROS: • For Industry – potential for a trial of shorter duration (dependent on relapse rate for the study population) **CONS:** • Possibility to leave DBT for OLE at 1st relapse (for ethical reasons) means that placebo-controlled safety/immunogenicity database will be limited and variable in duration • At end of trial, placebo patients will have different durations on study treatment (since relapsers can switch to study drug in OLE) thus interpretation of data is complicated by informative censoring • Evaluation of 2° endpoints is complicated by different durations of treatment and switch from placebo to active • Unable to demonstrate long-term efficacy after 1st relapse	**PROS:** • In theory, endpoint would allow collection of efficacy data (prevention of relapse = maintenance treatment) over a longer and fixed period of time – but probably not in practice • If patients required to stay on DBT for at least one year, better duration of placebo-controlled safety data might be available for comparison with study drug **CONS:** ---

TFR vs. ARR: Study Statistics (1)

TFR	ARR

PROS:
• Availability of powerful statistical techniques for survival analysis
  ▫ Kaplan Meier survival curves and the Cox model for multivariate analysis make the interpretation of results straightforward
  ▫ Censored data easily managed e.g. patients given rescue treatment by site without meeting protocol-defined criteria for relapse according to independent reviewers
	PROS:
	• Experience has been gained with this 1°endpoint as in MS trial
	• More data are available for ARR than TFR in NMO from publications but none describe controlled trials

TFR vs. ARR: Study Statistics (2)

TFR	ARR

CONS:
• Sample size calculations are based on assumptions since
  ▫ Few published data available on TFR in NMO
  ▫ Shape of distribution of post-baseline ARR has been assumed on the basis of MS trials because few NMO data are available
  ▫ Information on relationship between TFR and ARR in NMO is not available and TFR has been estimated from ARR, assuming shape of distribution of relapse-free rate
  ▫ Sample size calculations assumes constant hazard rate for TFR but clinical information is that relapses may cluster, occur after treatment change, or occur seasonally
	CONS:
	• Method does not give information on timing of relapse events
	• Methods of analysis of ARR do not easily allow for censored data
	• When follow up period is around one year and number of events per year is low, statistical power of ARR is lower than TFR e.g. if ARR 0.3, probability of a patient having 2 or more events in one year is 5% (Sormani et al 2013)
	• Less sensitive analysis method is likely to require larger numbers of patients in a small patient population

Pros and Cons of TFR vs. ARR as Primary Endpoint: Summary

1. Statistically there are pros and cons for both approaches
2. Practically and ethically TFR is a more attractive approach because patients can move to alternative treatment on relapse
3. Event-driven analysis is recommended in EMA draft Guidance for a condition which similarly affects the CNS irreversibly (e.g. stroke)

Definition/Measurement a relapse in NMO

- Acute and recurrent episodes of optic neuritis and transverse myelitis (“relapses”) is the defining characteristic of NMO as it leads to severe, permanent, relapse-related neurologic impairment such as blindness, paraplegia
- Considerations in the context of a clinical trial:
  - Evaluation of a relapse must be objective and measurable
  - What tool should be used to define a relapse in NMO?
  - Who should define a relapse?

Measurement of Relapse in NMO

- Kurtzke Expanded Disability Status Score (EDSS) is considered the gold standard for measuring the occurrence and severity of a neurological relapse
- Accepted by Regulatory Agencies as the appropriate tool evaluating changes in disability resulting relapses in MS studies
- EDSS is the most appropriate tool for assessment of occurrence of relapse and hence disability in NMO also

Measurement of Relapse – Discussion

- Timing of when should the EDSS be performed in relation to:
    1. Onset of symptoms and
    2. Timing of acute therapy for relapse
- What change is EDSS is considered a reliable, permanent and clinically meaningful change in disability?
- Who should perform the EDSS:
    1. Study physician or
    2. Independent adjudicator?
- Should other tools for measuring changes in disability in NMO other than EDSS?
- Should a co-primary endpoint be considered in NMO?
    - Lack of consensus on a single most important variable

Secondary Endpoints

- Support Primary Endpoint – more “holistic” characterisation of therapy benefit
- Important for Health Technology Assessment
- Differentiation from competitors

Secondary Endpoints to consider - Discussion

- ARR
- Severity of Relapse
- QoL
- Caregiver burden
- Other disability scores
- Others?

Confirmation of Risk/Benefit Post Approval - Discussion

- It is expected that post MAA surveillance will be required
  - Approval based on small population clinical trials (and exclusion of subpopulations) – ongoing risk/benefit monitoring (detect previously unrecognized positive or negative effects associated with a drug) has a greater imperative
- What are the appropriate methods for ongoing monitoring of efficacy and safety and pros/cons of each?
  - Further Trials and Meta analysis – unlikely unless conditional approval or significant risks in registration trial is identified
  - Epidemiological studies?
  - Patient registries for post-marketing research?
    - Disease vs. Drug Registries
  - Other types of active surveillance?
  - Passive surveillance appropriate?