10 November 2022
EMADOC-1700519818-959805
Executive Director

Letter of Support of Neurofilament light in childhood Neurological diseases

On 01/09/2021, the Applicant Amsterdam UMC requested scientific advice for their qualification object Neurofilament light in childhood Neurological diseases pursuant to Article 57(1)(n) of Regulation (EC) 726/2004 of the European Parliament and of the Council.

Neurofilament light protein in childhood Neurological diseases is intended as a biomarker to monitor disease activity that is related to axonal damage and to assess treatment responses in paediatric neurological diseases (<20 years old).

On 01/09/2022, the SAWP agreed on the advice to be given to the Applicant.

On 15/09/2022, the CHMP adopted the advice to be given to the Applicant.

Context

This concerns a qualification procedure for the use of neurofilament light chain (NfL) protein as a biomarker of axonal damage to monitor disease activity and to assess treatment responses in paediatric neurological diseases.

Neurofilament light chain (NfL) is a marker of neuroaxonal damage and therefore a potential marker of injury to the brain and spinal cord. It can be measured in the CFS, blood and plasma.

NfL is a major axonal cytoskeleton protein, especially expressed in long myelinated axons, which is released upon axonal damage. Elevations in CSF or blood NfL levels have been reported in multiple neurodegenerative diseases in adults, including multiple sclerosis (MS), Alzheimer's disease (AD) and central nervous system (CNS) infections. In addition, it has a major potential to monitor treatment and side-effects. However, little is known about NfL in paediatric neurological diseases.

NfL level has been evaluated as potential biomarker for disease activity and potential biomarker for treatment response in various paediatric neurological diseases i.e., SMA, CLN, MS, CLN2, MLD, Mitochondrial encephalopathy, among others. A high-level review of the literature was presented in the form of a review paper. The presented data suggests that NfL has a high face validity as a biomarker of disease.

Scientific discussion

Paediatric neurological disorders are complex and usually accopagnied by neuroaxonal damage. These occur at the cost of severe symptoms that impact daily life. Rarity and heterogeneity of these disorders pose a challenge to clinicians in terms of disease management and in development of treatments. A reliable and accurate quantification of neuroaxonal damage in these conditions may enable paediatric neurologists to make better-informed treatment decisions and measure effects of these under the assumption that axonal damage precedes or is closely related to signs and symptoms of the disease at stake.

However, many aspects require consideration before accepting NfL as a biomarker of disease staging, monitorimg disease progression or as biomarker of efficcay.

Context of use: NfL as monitor of disease activity

The intended context of use i.e. monitoring disease activity in paediatric neurological diseases accompanied by neuronal damage and evaluating responses to treatment is rather high level and does not fit well within the regular framework that is claim-based. Within the regular framework one would expect a more fine-tuned context of use i.e., as biomarker to select potential treatments in phase II studies which are worth to investigate further in phase III studies, as endpoint in dose-finding studies, as tool to enrich a study population, as secondary endpoints in clinical efficacy studies, as surrogate clinical endpoint and so on.

Another potential worthwhile application within the paediatric setting foreseen is the use as bridging endpoint allowing the extrapolation of clinical outcome results of a RCT in adults to children. If in that adult study the changes in clinical outcome and NfL correlate and this is also reflected in the treatment response, it migth be possible to brigde the clincal outcome in adults to that in children. Based on similar changes in NfL as compared to the adult clinical outcome study, a similar effect on clinical outcome may be assumed. The point is that all these foreseen contexts of use require a context-specific validation program. For instance, for NfL as prognostic marker to enrich study populations it should be shown that it is a prognostic marker for progression rate. Hence, the specific context of use within the regular framework needs discussion including the consequences for the further biomarker evaluation plan.

NfL increase occurs across a plethora of disorders, independent of the underlying pathology. The relationship between severity of the disorder and NfL levels is not clear. In Down Syndrome, the levels only increase in adulthood, while the neurodevelopmental delay occurs from early childhood. In SMA, levels do not correlate with SMN2 copies, and there is an inconsistent relation between SMA type and NfL levels. Whereas in more severe disease (SMA type 1) higher blood NfL levels are obsered as copared to SMA type 3, the CSF NfL is higher in SMA type 3 as compared to SMA type 1. A biological plausibility for this observation is lacking but it points at a more complex relationship between NFL and these phenotypes. Further, the median level and the range of levels vary significantly across different disorders and no specific pattern has been presented (for instance can NfL discriminate between acute or chronic trauma, or between demyelinating, degenerative or vascular disorders?). Thus, NfL levels do not simply correlate with disease severity within the same disorder and NfL levels cannot be harmonised across disorders.

NfL as marker for treatment responses

Few neurological disorders have available disease modifying drugs. In none of the studies presented, was the follow up of relevant length of time to ascertain that the magnitude of reduction of NfL is comparable to the magnitude of clinical response. Also, agents who require intrathecal administration (e.g., nusinersen) may modify the levels of NfL due to other mechanisms than the disease itself

(increased intracranial pressure, lumbar puncture, inflammatory reactions). Finally, other examples of markers of disease already proven in adults (beta-amyloid, tau [total or phosphorilated], alpha-synuclein) have failed to correlate well with clinical outcomes. So far there is insufficient evidence to consider NfL as a biomarker for response to treatment.

For the validation of NfL as surrogate endpoint replacing clinical outcome it would be required that 1) the treatment has a significant impact on the surrogate endpoint 2) treatment has a significant impact on the true clinical endpoint 3) the effect of treatment upon the true endpoint is captured by the surrogate (Prentice 1989, Molenbergs 2002). A simple correlation of NfL to a clinical endpoint would not be sufficient. This will require a prospective study on the natural history for disorders without specific treatments, or a therapeutic trial in disorders with approved agents.

Moreover, surrogacy in one condition does not necessarily imply demonstration of surrogacy in another condition. As stated earlier, the level of NfL elevation is quite different depending on the condition studied and so will be the disease activity-dependent fluctuations of NfL.

Overall the data in support of a qualification of NfL in paediatric neurological diseases are high-level and rather general with many uncertainties that need to be worked out further. These include among others:

- Normal values of NfL over age
- Discrimination of NfL values among normal subjects and subjects with neurological disease
- The normal range of NfL in subjects with non-CNS pathology and subjects with peripheral neuro-damage
- Discrimination of NfL values among subjects between different CNS neuropathologies
- Longitudinal fluctuation of NfL in normal subjects and subjects with CNS diseases
- Can NfL values discriminate between for various stages within the same condition
- Predictiveness of changes in NfL for clinical outcome per condition
- Can changes in NfL levels in a specific condition be attributed to a treatment effect

Further NfL is a molecule that leaks out of nervous system and is usually found in CSF (higher concentrations) or serum. Its clearance is not readily described and it is not clear whether children with comorbidities, namely renal or hepatic impairment, have different serum NfL behaviour.

Discussion/conclusion

NfL protein is positioned as a potential reliable indicator of axonal damage. It has a potential for monitoring disease activity of conditions associated with neurological axonal damage in general and even more so in paediatric neurological diseases. As such, the NfL can also be a potential biomarker to evaluate efficacy of treatments in paediatric neurological diseases.

This potential role of NfL as a relatively non-invasive biomarker to monitor disease activity that is associated with axonal damage and to assess treatment responses in paediatric neurological diseases is acknowledged. In the view that axonal damage is a possible substrate of the symptoms, reliable and accurate quantification of neuroaxonal damage in these diseases may enable paediatric neurologists to make better-informed treatment decisions and measure effects of these.

The current data in support of a qualification of NfL in paediatric neurological diseases are limited. So far the data does suggest that the evaluation of NfL as biomarker is more advanced in SMA and

multiple sclerosis. Instead of a broad claim the Applicant may consider focusing on the role of NfL in these conditions and expand the context of use to other disorders at a later point in the development.

In conclusion, the EMA acknowledged the potential of NfL as promising biomarker to quantify axonal damage and its several contexts of use especially in paediatric neurological diseases. Hence, the EMA has issued this Letter of Support to encourage the further development. However, the general context of use, i.e., montoring disease activivity without further refinement /specification, precludes a qualification opinin at this stage. The EMA is prepared to consider a future submission with a concrete feasible plan supported by sufficiently detailed protocols and procedures for a well-defined context of use.

The letter of support is issued on the basis of this qualification advice.

Yours sincerely,

Emer Cooke

Executive Director