06 November 2024
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Committee for Orphan Medicinal Products

Orphan designation withdrawal assessment report

Wainzua (Eplontersen)
Treatment of transthyretin-mediated amyloidosis
EU/3/23/2828

Sponsor: AstraZeneca AB

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Designated active substance(s)	Eplontersen sodium
Other name(s)	--
International Non-Proprietary Name	Eplontersen
Tradename	Wainzua
Orphan condition	Treatment of transthyretin-mediated amyloidosis
Sponsor's details:	AstraZeneca AB 151 85 Sodertalje Sweden
Orphan medicinal product designation procedural history	
Sponsor/applicant	AstraZeneca AB
COMP opinion	7 September 2023
EC decision	13 October 2023
EC registration number	EU/3/23/2828
Marketing authorisation	
Rapporteur / Co-rapporteur	Martina Weise / Ewa Balkowiec Iskra
Applicant	AstraZeneca AB
Application submission	05 October 2023
Procedure start	26 October 2023
Procedure number	EMA/H/C/006295/0000
Invented name	Wainzua
Proposed therapeutic indication	Eplontersen is indicated for the treatment of adult patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis (ATTRv) Further information can be found in the European public assessment report (EPAR) on the Agency's website: https://www.ema.europa.eu/en/medicines/human/EPAR/Wainzua
CHMP opinion	17 October 2024
COMP review of orphan medicinal product designation procedural history	
COMP rapporteur(s)	Joao Rocha / Judit Molnar
Expert	John Rusman
Sponsor's report submission	23 May 2024
COMP discussion and adoption of list of questions	08-10 October 2024
Oral explanation	05 November 2024
Sponsor's removal request	06 November 2024

2. Grounds for the COMP opinion

The COMP opinion that was the basis for the initial orphan medicinal product in 2023 designation was based on the following grounds:

- the intention to treat the condition with the medicinal product containing eplontersen was considered justified based on preliminary clinical data showing a clinically meaningful and statistically significant reduction from baseline in serum transthyretin concentration as well as a halting or slowing of polyneuropathy, as assessed by Modified Neuropathy Impairment Score +7 Composite Score;
- the condition is life-threatening and chronically debilitating due to the development of polyneuropathy and cardiomyopathy;
- the condition was estimated to be affecting not more than 1 in 10,000 persons in the European Union, at the time the application was made.
- In addition, although satisfactory methods of treatment of the condition exist in the European Union, the sponsor has provided sufficient justification for the assumption that the medicinal product containing eplontersen will be of significant benefit to those affected by the condition. The sponsor has provided preliminary clinical data that demonstrate that patients with Stage 2 transthyretin-mediated amyloidosis benefit from the eplontersen treatment. Specifically, an improvement in polyneuropathy as assessed by the Modified Neuropathy Impairment Score+7 when compared to authorised medicinal products has been shown. The Committee considered that this constitutes a clinically relevant advantage.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Transthyretin-mediated (ATTR) amyloidosis is a rare, progressive disease caused by the misfolding of the transthyretin (TTR) protein. This protein is primarily produced in the liver and normally helps transport vitamin A and thyroxine (a thyroid hormone) in the blood.

In ATTR amyloidosis, the misfolded TTR proteins aggregate into amyloid fibrils, which deposit in various tissues and organs, leading to their dysfunction. There are two main types of ATTR amyloidosis:

- Hereditary (hATTR): This form is caused by mutations in the TTR gene and can affect multiple organs. hATTR can be classified into cardiac, neurologic, or mixed forms, depending on the observed disease phenotype. Several TTR gene variants have been associated with hATTR, with the Val30Met variant being the most common worldwide. The Val30Met variant primarily causes neuropathic symptoms when associated with early disease onset (before 50 years of age), while both neurologic and cardiac involvement is observed in late-onset V30M. hATTR is generally inherited in an autosomal dominant pattern.
- Wild-type (wtATTR): This form occurs without any genetic mutations and primarily affects the heart. The average age at diagnosis for wtATTR is around 75 years and the great majority of cases reported are males. The condition has previously been known as Senile Systemic Amyloidosis.

The target patient population for eplontersen are patients with hereditary forms of the condition (hATTR), presenting with mild to moderate polyneuropathy. Around 60% of the pivotal study population with eplontersen carried the V30M mutation.

The intended therapeutic indication "*Wainzua is indicated for the treatment of hereditary transthyretin-mediated amyloidosis in adult patients with stage 1 or stage 2 polyneuropathy"* falls within the scope of the designated orphan condition "Treatment of transthyretin-mediated amyloidosis".

Intention to diagnose, prevent or treat

The medical plausibility has been confirmed by the positive benefit/risk assessment of the CHMP.

Chronically debilitating and/or life-threatening nature

ATTRv is a life-threatening and debilitating condition. ATTRv is a progressively debilitating disease that leads to premature death. Patients with ATTRv typically present with polyneuropathy, carpal tunnel syndrome, autonomic insufficiency, cardiomyopathy, and gastrointestinal features, occasionally accompanied by vitreous opacities and/or renal insufficiency. The clinical course of ATTRv usually progresses over 5 to 15 years and ends with death from cardiac failure, renal failure, or malnutrition (OMIM 105210). ATTRwt is also life-threatening, more common among elderly and men with a main clinical presentation of biventricular congestive heart failure. Cardiac symptoms are usually present when the amyloid deposits are extensive enough to produce an increase in left ventricular wall thickness. For patients with amyloid heart involvement due to ATTRwt-CM, median survival is approximately 60 months (Kyle et al 1996).

Since the original orphan designation, there have been no changes in the seriousness of ATTR amyloidosis and no new therapies improving the morbidity of the condition.

Number of people affected or at risk

At time of initial orphan designation in September 2023, the COMP agreed on a prevalence estimate of "not more than 1 in 10,000 persons" in the EU. This estimate was derived from the combined estimates for ATTRv-PN and ATTR-CM.

For ATTRv-PN, the prevalence estimate was 0.12 per 10,000 persons and mainly based on a global epidemiologic study by Schmidt and colleagues (Schmidt et al 2018), which included data/estimates from 20 EU countries. In the orphan maintenance report, this data source and estimate remains the same and values are reported in Table 1.

Table 1. Prevalence Estimates of ATTRv-PN for the European Union, Total and by Country (Schmidt et al 2018)

Country	General population, M	Prevalence low	Prevalence mid	Prevalence high	Source
Austria	8.6	3	13	65	Extrapolated
Belgium	11.3	4	17	85	Extrapolated
Bulgaria	7.2	41	41	41	Reported
Cyprus	1.2	51	51	51	Reported
Czech Republic	10.6	3	16	79	Extrapolated
Denmark	5.7	2	8	43	Extrapolated
Finland	5.5	2	8	41	Extrapolated
France	66.8	502	502	502	Reported
Germany	81.4	121	121	121	Reported
Greece	10.8	3	16	81	Extrapolated
Hungary	9.8	3	15	74	Extrapolated
Italy	60.8	500	550	600	Reported
Luxembourg	0.6	0	1	4	Extrapolated
Netherlands	16.9	45	45	45	Reported
Poland	38.0	12	56	286	Extrapolated
Portugal	10.3	1,990	2,051	2,111	Reported
Romania	19.8	6	29	149	Extrapolated
Slovenia	2.1	1	3	16	Extrapolated
Spain	46.4	15	69	349	Extrapolated
Sweden	9.8	253	253	253	Reported
Total Prevalence	**423.6**	**3,557**	**3,865**	**4,996**	**Calculated**
Prevalence per 10,000				**0.12**	**Calculated**

Data on the prevalence of ATTR-CM in the EU was derived from epidemiologic studies as reported by Lauppe et al (2022) and Damy et al (2020). At time of initial orphan designation in September 2023, a very conservative approach and using the highest prevalence in the published literature, ATTR-CM prevalence was estimated at 0.5 per 10,000. Now at time of orphan maintenance, the sponsor proposed a mean value of 0.39 per 10,000 for ATTR-CM, based on the same primary epidemiologic studies (Table 2).

Table 2. Prevalence Estimates of ATTR-CM for the European Union, Total and by Country

Country	General population, M	Prevalence per 100,000	Prevalence	Source	Citation
Denmark	5.8	1.4	81	Reported	Lauppe et al 2022
Finland	5.5	1.8	99	Reported	Lauppe et al 2022
France	64.1	4.2	2,694	Reported	Damy et al 2020
Norway	5.3	3.7	196	Reported	Lauppe et al 2022
Sweden	10.2	5.0	508	Reported	Lauppe et al 2022
Total	**90.9**		**3,578**		
Prevalence per 10,000			**0.39**	**Calculated**	

Due to the differences in choosing the highest vs the mean prevalence values for ATTR-CM, the previously proposed estimate for ATTR amyloidosis was slightly higher, i.e. 0.62 (ATTRv-PN: 0.12 per 10,000; and ATTR-CM: 0.5 per 10,000), vs the newly proposed estimate being slightly lower with 0.51 (ATTRv-PN:0.12 per 10,000; and ATTR-CM:0.39 per 10,000). Nevertheless, the primary epidemiologic data on which these estimates are based on remained the same between the initial orphan designation and orphan maintenance.

The sponsor states that since the original orphan drug designation application, 4 new papers on ATTR prevalence have been published. It is however not clear which papers these were, from which countries and what prevalence they reported.

The COMP notes that the sponsors newly proposed prevalence estimate for ATTR amyloidosis of 0.51 per 10,000 persons is much lower than the two recently accepted values for the initial orphan designations from July and September 2024, which agreed on a value of approximately 2 in 10,000 persons. In the orphan maintenance procedure for Amvuttra from September 2022, a prevalence estimate for ATTR amyloidosis of 1.8 per 10,000 persons was accepted.

While the specific prevalence values for ATTRv-PN were largely similar in these above mentioned recent orphan procedures to the one proposed by the sponsor (0.12 per 10,000), the prevalence values for ATTRwt were much higher with 1.7 per 10,000 persons as reported in the epidemiologic study by McDonagh (2021) or 1.91 per 10,000 persons, respectively, as reported in the epidemiologic study by Gertz and Dispenzieri (2020).

Considering the above, the COMP decided that a prevalence estimate of approximately 2 per 10,000 persons should be maintained, as it may better reflect the actual prevalence of the condition in the EU.

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

The current pharmacological treatments approved in the EU for ATTR are the TTR tetramer stabilising agent tafamidis and the TTR silencing agents inotersen, patisiran, and vutrisiran (Table 3):

Table 3. Authorised Medicines for the Treatment of ATTR

Proprietary name	Generic name	Therapeutic indication	MAA approval date in EU
VYNDAQEL	Tafamidis	Treatment of transthyretin amyloidosis in adult patients with Stage 1 symptomatic polyneuropathy to delay peripheral neurologic impairment (VYNDAQEL 20 mg soft capsules)	16 November 2011
		Treatment of wild-type or hereditary transthyretin amyloidosis in adult patients with cardiomyopathy (ATTR-CM) (VYNDAQEL 61 mg soft capsules)	
TEGSEDI	Inotersen	Treatment of Stage 1 or Stage 2 polyneuropathy in adult patients with hereditary transthyretin amyloidosis (hATTR)[a]	06 July 2018
ONPATTRO	Patisiran	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR)[a] in adult patients with Stage 1 or Stage 2 polyneuropathy	27 August 2018
AMVUTTRA	Vutrisiran	Treatment of hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) in adult patients with Stage 1 or Stage 2 polyneuropathy	15 September 2022

[a] hATTR or hereditary transthyretin-mediated amyloidosis is same as ATTRv

Since the initial orphan designation, no new authorised treatments for ATTR amyloidosis have become available.

For the purpose of this procedure, inotersen, patisiran, and vutrisiran are considered satisfactory methods as they have fully overlapping indication-wordings with eplontersen (i.e. treatment of patients with stage 1 and 2 polyneuropathy).

Tafamidis on the other hand is only authorized for the treatment of patients with stage 1 polyneuropathy. Therefore, eplontersen is considered to provide a benefit in a patient population which is not covered by the indication of tafamidis, i.e. stage 2 polyneuropathy. In the pivotal clinical study with eplontersen (ION-682884-CS3), around 20% of patients had stage 2 polyneuropathy at time of enrolment.

Significant benefit

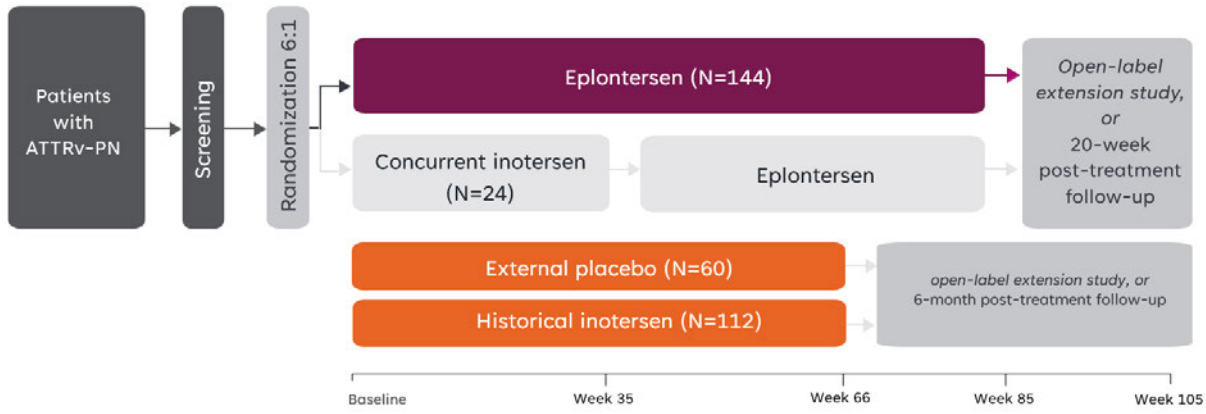
Protocol assistance has not been sought for the justification of significant benefit of eplontersen.

Of note, data directly comparing efficacy and safety between ATTR treatments are lacking.

The efficacy and safety of eplontersen was evaluated in a randomised, multicentre, open-label, trial (NEURO-TTRansform, ION-682884-CS3) that included a total of 168 adult patients with hereditary transthyretin-mediated amyloidosis with polyneuropathy (ATTRv-PN). Patients were randomised in a 6:1 ratio to receive subcutaneous injection of eplontersen 45 mg every 4 weeks (N=144) or inotersen 284 mg weekly (N=24) as a reference group. Of the 144 patients randomised to eplontersen, 140

(97.2 %) patients completed treatment through Week 35, 135 (93.8%) completed treatment through Week 65. Of note, 69.4% of patients had prior treatment with either tafamidis or diflunisal. The main comparison was between eplontersen and the external placebo group from the pivotal study for inotersen (NEURO-TTR, ISIS 420915-CS2). This CS2 study was a randomised, double-blind, placebo-controlled trial in adult patients with ATTRv-PN. That cohort received subcutaneous injections of placebo once weekly. Both studies employed identical eligibility criteria.

Figure 1. Study ION-682884-CS3 [CS3 study] schema (copied from CHMP assessment report)



ATTR-PN, transthyretin-mediated amyloidosis with polyneuropathy; N = number of patients in treatment group.

Eplontersen versus Inotersen

The sponsor claims that eplontersen offers clinically relevant advantages (CRA) over inotersen in the form of:

1. *greater potency in reducing serum TTR concentration;*
2. *improvement in patient-reported quality of life (Norfolk QoL-DN);*
3. *improved safety profile, specifically regarding severe thrombocytopenia and glomerulonephritis/renal function decline.*
4. *Furthermore, eplontersen offers improved contribution to patient care over inotersen due to a more convenient administration regimen that facilitates adherence to treatment.*

Data in support of claims:

1. The sponsor notes that eplontersen and inotersen are both ASO drugs targeting TTR mRNA but the GalNAc conjugation of eplontersen has significantly improved its potency over inotersen. This allows eplontersen to be administered at a dose that is 25-fold lower than that of inotersen by exposure. Mean inhibition of serum TTR are largely comparable between the two products.
2. Clinical efficacy: The pivotal clinical trials for the eplontersen (ION-682884-CS3) and inotersen (ISIS 420915-CS2) both included the same version of mNIS+7 composite score and Norfolk QoL-DN total score as pre-specified endpoints.

   The applicant conducted an indirect comparison between eplontersen and inotersen using a naïve side-by-side comparison regarding the observed change from baseline at Week 66 for mNIS+7 (eplontersen = 0.3 [95% CI -4.48 to 5.04]; inotersen = 5.8 [95% CI 1.59 to 10.00]) and Norfolk QoL-DN (eplontersen = -5.5 [95% CI -10.03 to -0.96]; inotersen = 0.99 [95% CI -3.19 to 5.18]. The applicant claims that these results **are suggestive** of greater stabilisation of neuropathy

impairment, and improved patient-reported quality of life with eplontersen (Benson et al 2018). Additionally, while treatment with inotersen appeared to be associated with maintenance of Norfolk QoL-DN scores through to Week 66, eplontersen appeared to improve Norfolk QoL-DN, indicating improved patient-reported quality of life with eplontersen.

3. Clinical safety: Data from ION-682884-CS3 indicates that eplontersen has a superior safety profile compared with inotersen. There were no cases of glomerulonephritis in eplontersen-treated participants. There was no clinically meaningful imbalance in liver function as assessed by hepatic AEs and clinical chemistry parameters versus external placebo. Non-serious and mild reported AEs of thrombocytopenia were reported in one participant in the eplontersen group and one participant in the external placebo group.

4. Major contribution to Patient Care (MCPC): Monthly administration of eplontersen via an autoinjector can be expected to improve ease-of-use and medication compliance.

COMP conclusion

The sponsor wishes to establish the significant benefit of eplontersen over inotersen by claiming all three different criteria, as set out in *Commission Notice (2016/C 424/03) on the application of Articles 3, 5 and 7 of Regulation (EC) No 141/2000 on orphan medicinal products*. The sponsor is reminded that the criteria for significant benefit are non-cumulative and a single claim supported with adequate data is sufficient to show that one of those criteria is satisfied (reference is also made to *Article 3(2) of Regulation No 847/2000)*. At present, none of the three criteria is sufficiently supported with data.

As regards the claim on CRA efficacy, the presented indirect comparison based on a naïve side-by-side comparison between arms from different clinical trials (NEURO-TTRansform and NEURO-TTR) does not allow the robust conclusions that eplontersen has a significant benefit of clinical efficacy over inotersen.

Notably, the applicant did not present a direct comparison that would be possible for endpoints measured until week 35 in the NEURO-TTRansform trial that included both an inotersen and an eplontersen arm. The presented naïve side-by-side comparisons do not quantify the uncertainty of the comparison (the indirectly estimated difference in effect between inotersen and eplontersen), neither do they take potential differences in the study population regarding prognostic or predictive factors into account.

To allow a comprehensive assessment of a potential significant benefit, the following analyses should be presented at least for the mNIS+7, the Norfolk QOL-DN score, the Symptom severity (NSC total scorea) and the Physical health–related quality of life (SF-36 PCS score) at week 35 and week 66:

a. A comparison of baseline characteristics between studies NEURO-TTR and NEURO-TTRansform for all study arms separately.

b. A replication of Figure 2 and 3 from this publication, including also the inotersen arms from both studies NEURO-TTR and NEURO-TTRansform (Eplontersen for Hereditary Transthyretin Amyloidosis With Polyneuropathy | Cardiology | JAMA | JAMA Network)

c. A direct comparison only based on study NEURO-TTRansform data between eplontersen and inotersen regarding all the above-mentioned endpoints for the available timepoints.

d. A network meta-analysis using IPD based on studies NEURO-TTR and NEURO-TTRansform regarding all the above-mentioned endpoints.

Furthermore, a discussion on the clinical relevance of the observed (numerical) differences is expected by the sponsor.

As regards the claim on CRA safety, a comprehensive quantitative comparison of the overall safety profile is expected to support any claims based on an improved safety. As a general observation, orphan designations which are based on the significant benefit criterion of improved safety are rare. The available safety data for eplontersen is still considered limited as compared to the overall pre- and post-marketing safety data available for inotersen, which is already authorized since July 2018. Furthermore, the sponsor is reminded that a claim of improved safety should primarily be based on clinical data and not non-clinical data.

As regards the claim of a MCPC, too little information (i.e. one sentence) is currently provided by the sponsor in support of this criterion. Firstly, according to the European Commission Notice (2016/C 424/03), a significant benefit claim based on MCPC can only be accepted if the new product has comparable efficacy (and safety) in relation to the satisfactory methods. While the data from the pivotal study (CS3) with eplontersen seems not to be suggestive of an inferior benefit/risk profile vis a vis inotersen, at least a brief discussion from the sponsor would have been expected to satisfy this prerequisite for a claim on MCPC. Secondly, while the patient advantage of a once monthly vs a once weekly SC injection may be considered self-evident, the sponsor is reminded that especially at time of orphan maintenance, data should be presented which demonstrates that such a change in dosing frequency translates into a reduction in patient burden. Such data has not been presented/discussed by the sponsor in this section.

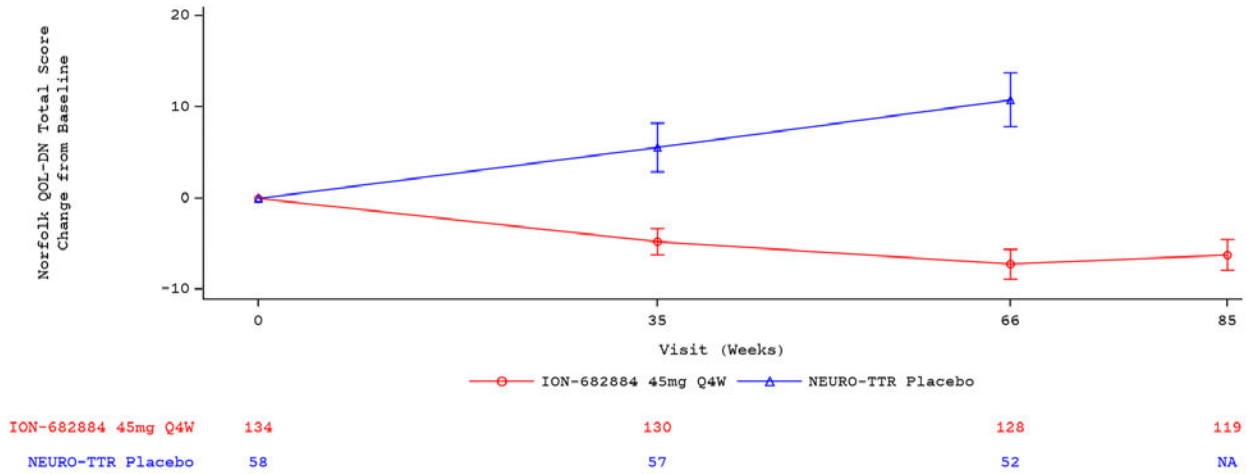
Eplontersen versus Patisiran

According to the sponsor eplontersen offers clinically relevant advantages over patisiran in the form of continued improvement in patient-reported quality of life (Norfolk QoL-DN total score) at Week 35 and through to Week 66. Importantly, eplontersen offers major contribution to patient care over patisiran in the form of lack of need for corticosteroids coadministration (thus avoiding potential risk of complications associated with chronic corticosteroid use), as well as self-administration via autoinjector and thus reduced healthcare system resource utilisation.

Data in support of claims:

Clinical efficacy: Eplontersen showed improvement in patient-reported quality of life (measured by Norfolk QoL-DN total score) at Week 35, with continued improvement through Week 66, offering a clinically relevant advantage over patisiran. In the APOLLO study in participants treated with patisiran, an initial improvement in Norfolk QoL-DN total scores was observed at Month 9 (corresponding to Week 36 to Week 39. However, this improvement did not continue from Month 9 to Month 18 (corresponding to Week 79 to Week 80 (Adams et al 2018).

Figure 2. Eplontersen quality of life: mean (± SE) of Norfolk QoL-DN Total Score Change From Baseline (Observed) Over Time up to Week 85 (On-Treatment) (Full Analysis Set; ION-682884-CS3)



ION-682884 45mg Q4W	134	130	128	119
NEURO-TTR Placebo	58	57	52	NA

Analysis is based on data collected up to 52 days after the last dose of the study drug. Only data up to Week 85 are included in the summary. Inotersen pivotal study ISIS 420915-CS2 provided data for external placebo group. Eplontersen dosing regimen was 45 mg Q4W.

MCPC: Patisiran is administered via intravenous infusion once every 3 weeks by a healthcare provider in a supervised setting while eplontersen is administered subcutaneously once per month. It is very commonly associated with injection-related reactions. As stated in the Summary of Product Characteristics, prior to each dose of patisiran, patients must be premedicated with an intravenous corticosteroid (dexamethasone 10 mg, or equivalent), oral paracetamol, and intravenous H1 and H2 blockers at least 60 minutes prior to the infusion in order to reduce the risk of injection-related reactions (ONPATTRO SmPC). Corticosteroid treatment can affect the skin, skeleton, muscles, eyes, central nervous system, metabolism, cardiovascular system, immune system, and gastrointestinal system. According to data from the Healthcare Cost and Utilization Project, corticosteroids in general were the most common cause of drug-related complications in 2004, accounting for 10% of all drug-related complications and 141000 hospital stays in the US (Elixhauser and Owens 2007). Evidence suggests that chronic corticosteroids, even at low or very low doses (as low as 1.5 mg of prednisone per day, or 45 mg per month), are associated with an increased risk of complications (Volmer et al 2018).

The sponsor further argues that eplontersen has clear advantages over patisiran as it can be self-administered once monthly and thus reduces healthcare system resource utilisation. The benefit of home administration for the patient is supported by a market research study carried out in 2023, where the need to rely on caregiver's help to get to and from doctor's appointments was one of the common challenges patients face living with ATTR. The sponsor referred to their Annex B document. Eplontersen is not associated with injection-related reactions, hence does not require any premedication. The lack of the need for co-administration of corticosteroids to manage injection-related reactions confers a clear safety advantage on eplontersen over patisiran, especially as a chronically administered therapy.

COMP conclusion

The sponsor wishes to establish the significant benefit of eplontersen over patisiran by claiming a clinically relevant advantage due to improved efficacy and a MCPC. Many of the above discussed aspects also apply here, particularly that significant benefit criteria are non-cumulative, suboptimal

data presentation/lack of comprehensive indirect treatment comparisons to provide more reassurance on the observed numerical treatment effect differences and lack of data to support the MCPC claim.

As regards the claim on CRA efficacy, the presented arguments and comparative efficacy data for eplontersen and patisiran are considered insufficient.

Two aspects are generally required:

1) Statistically robust quantification of the difference in effects (if needed with indirect comparison methods) and quantification of the uncertainty (95% confidence intervals)

2) An assessment whether the demonstrated difference is clinically meaningful.

In particular, 1) no actual data on the Norfolk QoL-DN total scores is presented for patisiran, only a reference to Adams and colleagues (2018); Instead, only a qualitative description of the long-term improvement is made but this effect has not been described quantitatively with an adequate quantification of both the difference in effect and the uncertainty of this estimate (including a comparison of the patient populations in the respective trials, use of statistical methodology that can adjust the indirectly estimated difference between the effects of patisiran and eplontersen for differences in prognostic and predictive variables and quantify the uncertainty of that estimated difference); and 2) the clinical relevance of such differences has not been discussed/established.

Both 1) and 2) need to be addressed by the sponsor.

As regards the claim of a MCPC, the sponsors main arguments comprise the general benefits of self-administration as compared to administration by caregiver/health-care professional, sparing of pre-medication especially corticosteroids due to injection-related reactions. While these arguments are well understood, two main aspects are considered missing: 1) data which demonstrates at least comparable efficacy (and safety) of eplontersen and patisiran; 2) data from patient reported outcomes (PRO) or patient preference survey data to support the claim for major contribution to patient care. Patients contributing to such a PRO or survey, respectively, should also have actual experience with eplontersen administration. In the market research study from the sponsor, 5 of the 9 patients with ATTR-PN were on current treatment with patisiran but none of the patients had ever received eplontersen. In this market research study, patients were only asked for their theoretical views about a product which resembles the eplontersen product profile (Product X). Such data is not considered sufficient to establish MCPC at time of orphan maintenance. The sponsor may wish to consult the published Orphan Maintenance Assessment Report for vutrisiran from 2022.

Eplontersen versus Vutrisiran

The sponsor claims that eplontersen offers clinically relevant advantages over vutrisiran in the form of:

1. *continued improvement in patient-reported quality of life (Norfolk QoL-DN total score) at Week 35 and through to Week 66; 2) no association with arthralgia and extremity pain. In addition, eplontersen offers improved contribution to patient care over vutrisiran due to lack of need for healthcare professional to administer and thus reduced healthcare system resource utilisation.*

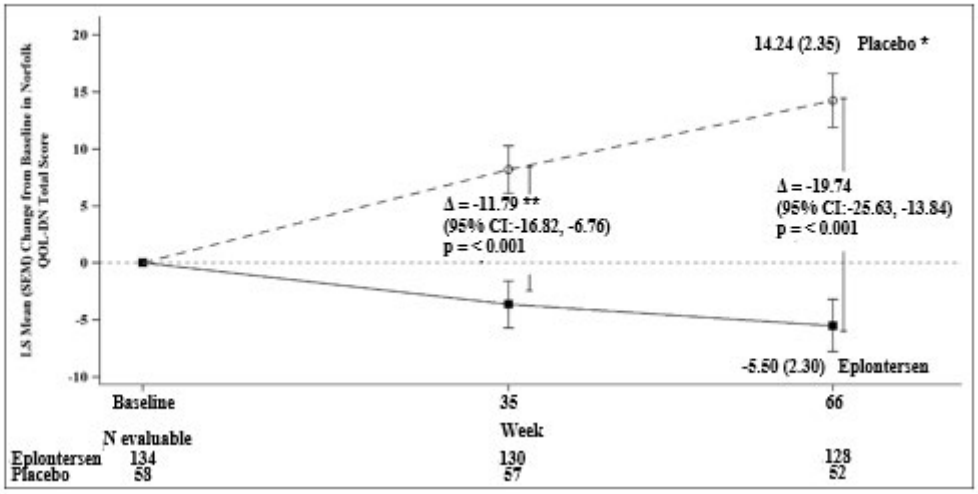
Data in support of claims:

Clinical efficacy: The mNIS+7 composite score used in the ION-682884-CS3 (eplontersen) and HELIOS-A (vutrisiran) clinical studies were different. The value of a comparison of this endpoint is therefore limited. Eplontersen showed improvement in patient-reported quality of life (measured by Norfolk QoL-DN total score) at Week 35, with continued improvement through Week 66 (Figure 1), offering a clinically relevant advantage over vutrisiran. In the HELIOS-A study in participants treated

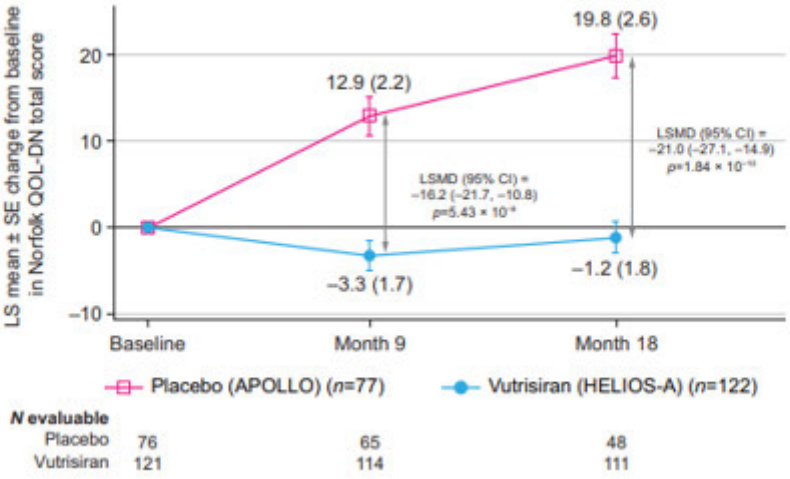
with vutrisiran, an initial improvement in Norfolk QoL-DN total scores was observed at Month 9 (corresponding to Week 36 to Week 39; Figure 2). However, this improvement did not continue from Month 9 to Month 18 (corresponding to Week 79 to Week 80; Adams et al 2023).

Figure 3. Norfolk QoL-DN Score: LS mean Change from Baseline Over Time with Eplontersen and Vutrisiran

Eplontersen



Vutrisiran



Eplontersen:
* External placebo group from another randomised controlled trial (NEURO-TTR).
** Treatment difference presents results from formal Week 35 interim analysis. Based on MI ANCOVA adjusted by propensity score weights with fixed categorical effects for treatment, disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline. Only data up to Week 35 are included in the Week 35 interim analysis.
Based on MMRM adjusted by propensity score weights with categorial effects for treatment, time, treatment-by-time interaction, and disease stage, Val30Met mutation, previous treatment, and fixed covariates for the baseline and the baseline-by-time interaction.
Analysis based on data collected up to 52 days after last dose of study treatment. Data up to Week 66 are included.
The Week 35 and Week 65 LS Mean treatment difference (Eplontersen - Placebo) with 95% CI (unadjusted) are presented.
Vutrisiran:
External placebo group from another randomised controlled trial (APOLLO).
The Norfolk QoL-DN data were calculated using the modified intent-to-treat population.
At baseline, the mean (SD) Norfolk QoL-DN score was 47.1 (26.3) in the vutrisiran group and 55.5 (24.3) in the external placebo group. Data at 9 months are from the ANCOVA/multiple imputation model and data at 18 months

are from the MMRM model.
Source: Figure 2B in Adams et al 2023.

Clinical safety: Vutrisiran is associated with 'very common' adverse drug reactions of arthralgia and pain in extremity (AMVUTTRA SmPC), both of which have been reported infrequently with eplontersen. Additionally, dyspnoea, and blood alkaline phosphatase increased occur as common adverse drug reactions with vutrisiran. Based on available safety information, including data from the ION-682884-CS3 study, eplontersen is not associated with any of these adverse events.

Major contribution to patient care: In contrast with vutrisiran, eplontersen can be administered without the need for a healthcare provider, and thus decreases healthcare utilisation and improves patient convenience as a result of administration in the home environment. Also, administration of eplontersen via an autoinjector can be expected to improve ease-of-use and medication compliance. The market research study showed that home administration can bring benefits to patients (e.g., alleviating financial and logistical burdens of travel to visits for drug administration), which are expected to also be relevant vs vutrisiran. However, only one patient in the study was on vutrisiran.

COMP conclusion

The sponsor wishes to establish the significant benefit of eplontersen over vutrisiran based on all three different criteria, i.e. a clinically relevant advantage due to improved efficacy and improved safety, as well as a MCPC. Many of the above discussed aspects also apply here, particularly that significant benefit criteria are non-cumulative and suboptimal data presentation/lack of comprehensive indirect treatment comparisons to provide more reassurance on the observed numerical treatment effect differences and lack of data to support the MCPC claim.

As regards the claim on CRA improved efficacy, the comparative efficacy data for eplontersen and vutrisiran are considered insufficient.

In particular, 1) the long-term improvement of patients quality of life, as assessed by the Norfolk QoL-DN total score shows a greater treatment effect relative to the placebo group for vutrisiran, at both respective assessment timepoints (month 9, mean change from baseline: −3.3 [vutrisiran] and +12.9 [placebo]; mean difference [95% CI]: −16.2 [−21.7, −10.8]and moth 18 mean change from baseline: −1.2 [vutrisiran] and 19.8 [placebo]; LS mean difference [95% CI]: −21.0 [−27.1, −14.9]-) as compared to eplontersen (week 35: adjusted mean change from baseline -3.6 [eplontersen] and 8.2 [placebo] with adjusted mean difference [95% CI] −11.6 [−16.9, −6.8], week 66: adjusted mean change from baseline −5.5 [eplontersen] and 14.2 [placebo] with adjusted mean difference [95% CI] −19.7 [−25.6, −13.8]); this was not discussed by the sponsor;

2) only a qualitative description of the long-term improvement is made but the difference between vutrisiran and eplontersen has not been described quantitatively with an adequate quantification of both the difference in effects and the uncertainty of this estimate (including a comparison of the patient populations in the respective trials, use of statistical methodology that can adjust the indirectly estimated difference between the effects of Vutrisiran and eplontersen for differences in prognostic and predictive variables and quantify the uncertainty of that estimated difference); and

3) the clinical relevance of the claimed improved long-term trends in the quality-of-life scores have not been discussed/ established and neither have the patient populations in the respective trials been compared. All three points 1), 2) and 3) need to be addressed by the sponsor.

As regards the claim on CRA improved safety, a comprehensive quantitative comparison of the overall safety profile is expected by the COMP to support any claims based on an improved safety. As a

general observation, orphan designations which based the significant benefit on the criterion of improved safety are rare.

As regards the claim of a MCPC, the sponsors main arguments comprise the general benefits of self-administration as compared to administration by a caregiver/health-care professional which may translate into improved medication compliance. While these arguments are well understood, two main aspects are considered missing: 1) data which demonstrates at least comparable efficacy (and safety) of eplontersen and vutrisiran; 2) data from patient reported outcomes (PRO) or patient preference survey data to support the claim for major contribution to patient care. Patients contributing to such a PRO or survey, respectively, should also have actual experience with eplontersen administration. As pointed out by the sponsor themselves, in the market research study only one patient received vutrisiran and none of the patients had ever received eplontersen. In this market research study, patients were only asked for their theoretical views about a product which resembles the eplontersen product profile (Product X). Such data is not considered sufficient to establish MCPC at time of orphan maintenance. The sponsor may wish to consult the published Orphan Maintenance Assessment Report for vutrisiran from 2022. Furthermore, no data on improved compliance to eplontersen vis a vis vutrisiran has been presented. The COMP also noted that while the (draft) SmPC for eplontersen includes guidance for patients who wish to self-administer, it needs to be administered more frequently than vutrisiran, i.e. once monthly vs once every 3 months. Both products are for subcutaneous administration.

Overall COMP conclusion

The significant benefit of eplontersen over inotersen, patisiran, and vutrisiran is not considered established. At time of initial orphan designation in 2023, significant benefit was based on CRA improved efficacy, i.e. improvement in polyneuropathy as assessed by the Modified Neuropathy Impairment Score+7 when compared to inotersen, patisiran, and vutrisiran. The COMP emphasizes that at time of orphan maintenance more robust data is expected to substantiate claims on significant benefit.

The COMP adopted a list of questions on significant benefit.

4. COMP list of issues

Significant benefit

The sponsor is invited to provide additional data to support the significant benefit of eplontersen over inotersen, patisiran, and vutrisiran, in line with the detailed comments made in the respective above paragraphs ("COMP conclusion").