

**NIHR Innovation Observatory
Evidence Briefing: October 2017****NEOD001 for amyloid light-chain (AL) amyloidosis**

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LAY SUMMARY

Amyloid light-chain (AL) amyloidosis is caused by a bone marrow disorder. In AL amyloidosis, plasma cells (a type of white blood cell) from bone marrow produce misfolded light-chain protein, that when aggregated is called amyloid. These amyloid proteins accumulate in the bloodstream and are deposited on tissues, nerves and organs, stopping normal function and leading to organ failure. AL amyloidosis can affect any organ apart from the brain, and most commonly affects the heart and kidneys. Around 330 cases are diagnosed each year; two-thirds of patients are male, and the condition usually affects people aged 50-80 years.

Current treatments for AL amyloidosis target the plasma cells in the bone marrow, stopping the production of amyloid. NEOD001 has the potential to target amyloid protein directly in the bloodstream as well as within the organs. It would make the amyloid protein that is in the bloodstream ineffective, and would also clear amyloid protein deposits in tissues, nerves and organs. This has the potential to be the first treatment for AL amyloidosis that could restore organ function. NEOD001 is given by intravenous infusion once every 28 days.

This briefing is based on information available at the time of research and a limited literature search. It is not intended to be a definitive statement on the safety, efficacy or effectiveness of the health technology covered and should not be used for commercial purposes or commissioning without additional information.

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TARGET GROUP

Amyloid light-chain amyloidosis and cardiac dysfunction.

TECHNOLOGY

DESCRIPTION

NEOD001 is being developed as a potential first-in-class, disease-modifying agent for the treatment of AL amyloidosis. In this condition plasma cells from bone marrow over-produce light chain proteins that misfold and aggregate, resulting in the formation of soluble toxic aggregates and insoluble deposits (amyloid). NEOD001 is a monoclonal antibody directed against the misfolded forms of this protein that are responsible for the organ dysfunction that cause morbidity and mortality in this disease.¹ NEOD001 neutralizes soluble toxic aggregates, and induces clearance of insoluble deposited fibrils (amyloid) through phagocytosis.²

In the Phase IIb trial (PRONTO; NCT02632786), NEOD001 is administered by intravenous (IV) infusion at 24mg/kg once every 28 days for 12 infusions.³ In the phase III trial (VITAL; NCT02312206), NEOD001 is administered by IV infusion at 24mg/kg once every 28 days.⁴

NEOD001 does not currently have Marketing Authorisation in the EU for any indication.

INNOVATION and/or ADVANTAGES

Current treatment strategies for AL amyloidosis target plasma cells to reduce amyloid production by using chemotherapy. At present no treatment is available that has a direct effect on amyloid deposits. NEOD001 is designed to specifically target the amyloid deposits that accumulate in patients with AL amyloidosis.⁵ Pre-clinical testing has demonstrated that NEOD001 reacts only with a “cryptic” epitope found on the mis-folded light chain and does not interact with normally folded light chain.¹

The drug also acts by neutralising the circulating soluble amyloid and clearing the deposited insoluble amyloid that accumulates within affected organs. This not only checks the progression of AL amyloidosis, but improves organ function by reducing the amount of amyloid in the organs.⁵

If licensed, NEOD-001 will offer a new treatment option for patients with AL amyloidosis, who currently have few effective therapies available. It would also be the first treatment with the potential to restore organ function for these patients.

DEVELOPER

Prothena Therapeutics Ltd

AVAILABILITY, LAUNCH or MARKETING

NEOD001 was designated an orphan drug in the EU for AL amyloidosis in August 2013.

NEOD001 was designated an orphan drug in the USA for AL amyloidosis in February 2012.

NEOD001 was granted Fast Track status in the USA for AL amyloidosis in December 2014.

PATIENT GROUP

BACKGROUND

AL amyloidosis (also known as primary systemic amyloidosis) is caused by misfolding and aggregation of a protein produced by abnormal cells in the bone marrow. It is not considered to be hereditary, although some families have an increased incidence of blood diseases including myeloma, lymphoma and AL amyloidosis. Around 15% of patients who are diagnosed with multiple myeloma will also acquire AL amyloidosis, and currently available treatments for both conditions are similar, although AL amyloidosis is not classified as a bone marrow cancer. Approximately two-thirds of patients are male, and the condition usually affects people aged 50-80 years.⁶

In AL amyloidosis, plasma cells from bone marrow over-produce abnormal light chain proteins that misfold, resulting in the formation of amyloid. These misfolded amyloid proteins build up in the bloodstream and deposit on tissues, nerves and organs, impeding normal function and leading to organ failure. AL amyloidosis can impact multiple organs including the heart, kidney, liver, skin, gastrointestinal tract, and/or the autonomic or peripheral nerves.^{1,6}

AL amyloidosis is often difficult to recognise because of its broad range of manifestations and what are often vague symptoms.⁷ The symptoms depend on which organs are affected by the amyloid deposits, and the degree to which organ function is impaired. Fatigue, weight loss and swelling are the most common symptoms, although patients can also present with flu-like symptoms or diarrhoea.⁶ The organs most frequently affected in AL amyloidosis are the kidneys and heart; the condition can occur anywhere in the body apart from the brain. The vague nature of symptoms frequently leads to delays in diagnosis such that organ dysfunction is advanced by the time treatment is initiated.⁷ Diagnostic testing involves blood tests, urine tests, tissue biopsies, and bone marrow aspirate/biopsy, in addition to tests on the affected organs (e.g. echocardiogram to look for evidence of amyloid deposits in the heart) or organ biopsies. When a diagnosis is made early, before advanced organ dysfunction ensues, improvement in organ function and prolonged survival are possible.⁶

CLINICAL NEED and BURDEN OF DISEASE

The UK National Amyloidosis Centre diagnoses around 600 new cases of amyloidosis each year, of which around 55% (330 cases) are AL amyloidosis.⁸

AL amyloidosis is usually a very serious condition which, if left untreated, is progressive and typically fatal within 5 years.⁸ Involvement of the heart is the commonest cause of death in AL amyloidosis and is a major determinant of prognosis. The prognosis among affected patients with markedly elevated brain natriuretic peptide (BNP) and cardiac troponin (Mayo stage III disease) is around 8 months.⁹

Successful treatment inhibits progression of the disease and can result in regression of existing amyloid deposits; the success rate varies between treatments but is about 40% to 60% on average. Approximately 20-30% of patients can expect to benefit greatly from low-dose chemotherapy after they have taken it for one year. The results from stem-cell transplantation suggest that more than 50% of patients respond very favourably within 6-12 months.⁸

Across all types of amyloidosis (primary diagnosis ICD-10 code E85 Amyloidosis), there were 2,620 hospital admissions in England in 2015/16, resulting in 6,716 bed days. Of these admissions, 2,011 were day cases.¹⁰

The number of prevalent AL amyloidosis patients with cardiac dysfunction, previously treated potentially eligible for NEOD001 can be estimated in the range between 462 and 554. These numbers are based on the following assumptions: the UK National Amyloidosis Centre (NAC) diagnoses around 600 new cases of amyloidosis each year, of which around 55% (330 cases) are AL amyloidosis; 50-60% of newly diagnosed AL Amyloidosis patients presents with cardiac dysfunction¹¹ resulting in 165-198 new AL amyloidosis patients with cardiac dysfunction per year; up to 1/3 of newly diagnosed patients die in the first year of diagnosis from progressive cardiomyopathy, leaving 116-139 patients with AL Amyloidosis with cardiac dysfunction, previously treated per year. The mean overall survival (OS) for AL amyloidosis is 4 years¹², leading to an estimated prevalence of 462-554 patients in UK eligible for treatment with NEOD001.^a

PATIENT PATHWAY

RELEVANT GUIDANCE

NICE GUIDANCE

No guidance has been published by NICE for amyloid light-chain amyloidosis.

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard Contract for Diagnostic Service for Amyloidosis (All Ages). E13/S(HSS)/c.

OTHER GUIDANCE

- British Society for Haematology. Guidelines on the diagnosis and investigation of AL amyloidosis. October 2014.
- British Society for Haematology. Guidelines on the management of AL amyloidosis. October 2014.

CURRENT TREATMENT OPTIONS

Current treatment of AL amyloidosis is directed at the underlying bone marrow disorder, targeting the plasma cell clone using therapies and regimens approved for patients with multiple myeloma. At present no drug is available that has a direct effect on amyloid deposits, and current treatments are aimed at reducing the amount of the particular amyloid-forming protein in the bloodstream. If new amyloid deposition can be completely halted, up to 50% of the existing amyloid deposits can disperse each year; regression of amyloid is usually associated with improvement in general wellbeing as well as stabilisation or recovery of organ function. Unfortunately, organs that have been severely damaged

^a Information provided by company.

before treatment may continue to deteriorate despite new amyloid deposition having been completely stopped.⁸

Guidelines published in the British Journal of Haematology recommend:

- Treatment of AL amyloidosis is based on anti-myeloma therapy but there is no standard treatment and it has to be tailored to the individual patient in terms of their age, comorbidities, extent of organ involvement and patient's wishes with the treatment goal to achieve a very good partial response or better, if possible.¹³
- First line treatment is recommended with combination chemotherapy regimens similar to those used in myeloma but typically using dexamethasone. Proteasome inhibitor-based regimens are a preferred choice due to better response rates and outcomes in phase II studies and a bortezomib-alkylator-steroid combination is preferred where a rapid response is desirable (cardiac involvement, renal impairment, severe hypoalbuminaemia, fluid retention). There is greater treatment-related toxicity in patients with AL amyloidosis compared to that seen in patients with multiple myeloma and dose reductions are required.
- There is no standard treatment at relapse. Treatment needs to be tailored to the individual patient and agents not previously used are usually preferred. However previously-used treatments may be used again if associated with a good prolonged response and if well tolerated.

Information published by the Centre for Amyloidosis and Acute Phase Proteins states:

- The main treatment for AL amyloidosis is chemotherapy, with the aim of decreasing the number of abnormal plasma cells, which will proportionately reduce production of the amyloid-forming light chain protein, and may allow existing amyloid deposits to regress.⁸
- Intermediate dose combination chemotherapy is the recommended first-line treatment for most patients. Treatment is given in between 4 and 6 monthly cycles, and beneficial effects are seen in some patients within 6 months of starting treatment. This type of treatment is successful in halting production of abnormal light chain in nearly 50% of patients. The light chain response is usually assessed after three months, and treatment can be adjusted according to response, adverse effects and personal preferences.⁸
- Low dose tablet chemotherapy is recommended for fewer than 10% of patients. It is often necessary to continue this type of treatment for 18 months, and it is successful in only about 20-30% of cases. As this treatment gradually depletes bone marrow reserves, it may exclude subsequent stem cell transplantation.⁸
- High dose IV chemotherapy is rarely recommended as a first-line treatment. This treatment usually requires "stem-cell rescue" (commonly referred to as autografting or autologous stem cell transplantation). This treatment is better suited to younger patients and those who do not have serious amyloid disease in several organs. Approximately two-thirds of patients benefit substantially from this type of treatment, and some patients improve considerably within 3-6 months. The main drawback is the rise of serious adverse effects and even death in about 10-30% of those with amyloidosis, but the risk is lower in certain groups of patients.⁸

Following chemotherapy the improvement in amyloid-related symptoms is often slow, and may not be apparent for 12-18 months.⁸ Patients are followed for the presence of a hematologic response based on the reduction of abnormal light chain. For patients that do achieve a complete hematologic response, a minority will achieve improvement in organ function, and when it occurs is generally within several months although in rare cases improvement may be delayed.¹⁴

Treatment may also be required for the organs affected by AL amyloidosis (supportive treatment), such as diuretics or ACE inhibitors for cardiac or renal problems.⁷ Kidney/heart transplantation may be required for patients with irreversible organ damage.¹⁵

EFFICACY and SAFETY

Trial	VITAL, NCT02312206, NEOD001-CL002, EudraCT-2014-003865-11; NEOD001 plus standard of care vs placebo plus standard of care; phase III
Sponsor	Prothena Therapeutics Ltd
Status	Ongoing
Source of Information	Trial registry ⁴ , Company
Location	EU (incl UK), USA, Canada, Australia, Israel
Design	Randomised, placebo-controlled
Participants	N=260; aged ≥18 years old; amyloid light-chain amyloidosis; newly-diagnosed or treatment naive
Schedule	Randomised to 24mg/kg (maximum dose of 2,500mg) of NEOD001 administered once every 28 days; or placebo administered as a 250ml bag of normal saline once every 28 days.
Follow-up	Subjects will remain on-study until study completion, which will occur when approximately 156 primary endpoint events (all-cause mortality or cardiac hospitalisation as adjudicated by the Clinical Endpoint Committee [CEC]) have been reached. All subjects who discontinue will be followed until the last event is adjudicated. All eligible subjects are enrolled into open-label extension studies.
Primary Outcomes	Time to all-cause mortality or cardiac hospitalisation as adjudicated by the CEC. In addition, the components of the primary endpoint will be analyzed separately. Only cardiac hospitalizations occurring >90 days after start of treatment will be included in these analyses.
Secondary Outcomes	Key Secondary <ul style="list-style-type: none"> • Change from baseline to Mth 9 in the SF-36v2 Physical Component Summary (PCS) score • Change from baseline to Mth 9 in the 6MWT distance (meters) • NT-proBNP (cardiac) best response from baseline through Mth 9 Additional Secondary <ul style="list-style-type: none"> • For renal evaluable subjects, renal best response from baseline through Mth 9 • For peripheral neuropathy evaluable subjects, change from baseline to Mth 9 in NIS-LL total score

	<ul style="list-style-type: none"> For hepatic evaluable subjects, hepatic best response from baseline to Mth 9
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Q2 2019

Trial	PRONTO, NCT02632786, NEOD001-201, EudraCT-2015-004318-14; NEOD001 vs placebo; phase IIb	NCT03154047, NEOD001-OLE251, EudraCT-2016-004664-18; NEOD001; phase IIb extension
Sponsor	Prothena Therapeutics Ltd	Prothena Therapeutics Ltd
Status	Ongoing	Ongoing
Source of Information	Trial registry ⁴ , Company	Trial registry ⁴ , Company
Location	EU (incl UK), USA, Australia, Israel	EU (incl UK), USA, Australia, Israel
Design	Randomised, placebo-controlled	Open-label extension study
Participants	N=129; aged ≥18 years old; amyloid light-chain amyloidosis who had a haematologic response to previous treatment for their amyloidosis (e.g. chemotherapy, autologous stem cell transplant) and have persistent cardiac dysfunction	Subjects with amyloid light-chain amyloidosis who completed Study NEOD001-201 (PRONTO)
Schedule	Randomised to 24mg/kg (not to exceed 2,500mg) of NEOD001 administered once every 28 days; or placebo administered as infusion of normal saline once every 28 days.	NEOD001 24mg/kg (not to exceed 2,500mg) administered as an IV infusion once every 28 days.
Follow-up	Active treatment for 12 mths. All eligible subjects are enrolled into open-label extension studies.	Active treatment for up to 38 mths
Primary Outcomes	<ul style="list-style-type: none"> Cardiac response as defined by NT-proBNP best response from baseline through 12 mths of treatment 	<ul style="list-style-type: none"> Long-term safety and tolerability as assessed by vital signs, 12-lead ECGs, routine clinical laboratory assessments and adverse events Immunogenicity
Secondary Outcomes	<p>Key Secondary</p> <ul style="list-style-type: none"> Change from baseline to 12 months of treatment in the 	<ul style="list-style-type: none"> N-terminal pro-brain natriuretic peptide (NT-proBNP)

	<p>Physical Component Summary (PCS) score of the Short Form-36v2 (SF-36v2)</p> <ul style="list-style-type: none"> • Change from baseline to 12 months of treatment in the 6MWT distance (meters) • NT-proBNP slope over 12 months of treatment <p>Additional Secondary</p> <ul style="list-style-type: none"> • For renal evaluable subjects, renal best response from baseline through 12 months of treatment • For peripheral neuropathy evaluable subjects, change from baseline to 12 months of treatment in Neuropathy Impairment Score – Lower Limbs (NIS-LL) total score • For hepatic evaluable subjects, hepatic best response from baseline through 12 months of treatment 	<ul style="list-style-type: none"> ○ Response ○ Best response from baseline ○ Change from baseline <ul style="list-style-type: none"> • Change from baseline in troponin T • Change from baseline in the Short Form-36 Health Survey version 2 (SF-36v2) Physical Component Summary (PCS), Mental Component Summary (MCS), and the 8 subscales • Change from baseline in the 6-Minute Walk Test (6MWT) distance (meters) • For renal-evaluable subjects: <ul style="list-style-type: none"> ○ Renal response ○ Renal best response from baseline ○ Change from baseline in creatinine, proteinuria, and eGFR • For peripheral neuropathy-evaluable subjects: <ul style="list-style-type: none"> ○ Change from baseline in Neuropathy Impairment Score-Lower Limbs (NIS-LL) total score • For hepatic-evaluable subjects: <ul style="list-style-type: none"> ○ Hepatic response ○ Hepatic best response from baseline • Time to all-cause mortality (overall survival)
Key Results	-	-
Adverse effects (AEs)	-	-
Expected reporting date	Q2 2018	Q3 2021

ESTIMATED IMPACT

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

- | | |
|--|--|
| <input checked="" type="checkbox"/> Reduced mortality/increased length of survival | <input checked="" type="checkbox"/> Reduced symptoms or disability |
| <input type="checkbox"/> Other | <input type="checkbox"/> No impact identified |

IMPACT ON HEALTH and SOCIAL CARE SERVICES

- | | |
|---|---|
| <input type="checkbox"/> Increased use of existing services | <input type="checkbox"/> Decreased use of existing services |
| <input type="checkbox"/> Re-organisation of existing services | <input type="checkbox"/> Need for new services |
| <input type="checkbox"/> Other | <input checked="" type="checkbox"/> None identified |

IMPACT ON COSTS and OTHER RESOURCE USE

- | | |
|---|---|
| <input type="checkbox"/> Increased drug treatment costs | <input type="checkbox"/> Reduced drug treatment costs |
| <input type="checkbox"/> Other increase in costs | <input type="checkbox"/> Other reduction in costs |
| <input checked="" type="checkbox"/> Other: <i>uncertain unit cost compared to existing treatments</i> | <input type="checkbox"/> None identified |

OTHER ISSUES

- | | |
|---|---|
| <input type="checkbox"/> Clinical uncertainty or other research question identified | <input checked="" type="checkbox"/> None identified |
|---|---|

REFERENCES

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