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Biotin for Adrenomyeloneuropathy without cerebral involvement

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LAY SUMMARY

Adrenomyeloneuropathy is an inherited condition of the nervous system. It is characterised by progressive stiffness and weakness of the legs, gait imbalance and pain in the lower limbs. Adrenomyeloneuropathy is an adult form of adrenoleukodystrophy, which has an estimated birth incidence of one in twenty thousand. Adrenomyeloneuropathy manifests in more than sixty percent of female patients in adulthood and in nearly all male patients who reach adulthood.

High dose pharmacy-grade biotin is under evaluation for the treatment of adrenomyeloneuropathy. Biotin is also known as Vitamin H or Vitamin B7. This treatment could lead to a clinical improvement in walking of patients who are affected by the condition. In the phase III clinical trial, biotin is administered orally at 100mg three times a day for twenty-four months. Current treatments are limited to those which address symptoms of the condition and active physical rehabilitation.

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TARGET GROUP

Adrenomyeloneuropathy (without cerebral involvement) aged 18-60 years.

TECHNOLOGY DESCRIPTION

Biotin (MD1003; Coenzyme R; D-biotin Vitamin H) is an active pharmaceutical ingredient thought to have both pro-myelinogenic effects and to enhance the supply of energy for nerve impulse transmission.[1] Biotin has a mode of action which potentially influences the following targets: (i) it activates acetyl-CoA carboxylases (ACC1 and ACC2), the rate-limiting enzymes in the synthesis of fatty acids required for myelin synthesis, and (ii) it activates the Krebs cycle in demyelinated axons to increase energy production.[1]

Alternative treatment options for adrenomyelonopathy (AMN) are often limited to the treatment of symptoms (e.g. medications against spasticity, sphincter dysfunctions, impotence and neuropathic pain) and active physical rehabilitation.[2] Lorenzo's Oil is currently under investigation as a treatment for AMN. This is a 4:1 mixture of glyceryl trioleate and glyceryl trierucate, which, when given orally and combined with a diet reduction of very long-chain fatty acids (VLCFA), has been shown to normalize the level of VLCFA in plasma.[2]

In the phase III trial, biotin is administered orally at 100mg three times a day for 24 months.[3]

Biotin is in phase III development for AMN, primary progressive multiple sclerosis and secondary progressive multiple sclerosis. Phase II trials are being conducted for amyotrophic lateral sclerosis and chronic inflammatory demyelinating polyneuropathy.[4]

INNOVATION and/or ADVANTAGES

Current treatments for AMN are limited to those which address symptoms of the condition and active rehabilitation.[2] If licensed, biotin will offer an additional treatment option for patients with AMN.

DEVELOPER

MedDay Pharmaceuticals SA

BACKGROUND

Adrenomyeloneuropathy (AMN) is an inherited condition that affects the spinal cord. It is a form of X-linked adrenoleukodystrophy (X-ALD) which is a rare neurodegenerative disorder, caused by mutations of the ABCD1 gene, which results in loss of function of the encoded adrenoleukodystrophy protein (ALDP).[2] Because the gene defect is located on the X chromosome, males are usually more affected than women (who have two copies of the X chromosome).[2] AMN (the most frequent adult form of X-ALD) manifests in more than 60% of female X-ALD patients in adulthood and nearly all male X-ALD patients who reach adulthood.[2] ALDP deficiency impairs the metabolism of very long-chain fatty acids, resulting in their accumulation in plasma and tissues.[2] Virtually all males with X-ALD who develop AMN in adulthood, usually do so in the 3rd or 4th decade. Initially, the neurologic disability is slowly progressive. As a consequence of spinal cord involvement, males with AMN develop progressive stiffness and weakness of the legs, gait imbalance, pain in the lower limbs and sphincter

disturbances (mostly urinary).[2] Sensory ataxia, faecal incontinence and pain in the legs are often more prominent in symptomatic women with AMN.[5]

Signs and symptoms of AMN vary, but may include:

- Difficulty walking
- Changes in gait (style of walking)
- Progressive stiffness and weakness of the legs
- Ataxia
- Hypertonia
- Speech difficulties
- Adrenal insufficiency
- Sexual dysfunction and/or impotence
- Problems with bladder control
- Mild peripheral neuropathy
- Weight loss
- Nausea[6]

In addition to the symptoms above, people with AMN with cerebral involvement may develop behavioural abnormalities, vision loss, hearing problems and/or seizures.[6]

CLINICAL NEED and BURDEN OF DISEASE

X-linked adrenoleukodystrophy (X-ALD) is the most common peroxisomal disorder.[5] The estimated birth incidence of X-ALD is 1 per 20,000 births.[a,7] AMN manifests in more than 60% of female patients in adulthood and nearly all male patients who reach adulthood.[7] In 2015-16, there were 268 hospital admissions, 310 finished consultant episodes and 952 bed days due to disorders of fatty-acid metabolism (ICD code: E71.3) in England.[8]

RELEVANT GUIDANCE

NICE GUIDANCE

- NICE guideline (NG 42). Motor neurone disease: assessment and management. February 2016

NHS ENGLAND and POLICY GUIDANCE

- NHS England. 2013/14 NHS Standard contract for medical genetics (all ages). E01/S/a

[a] Estimated general birth incidence; burden of disease data are unavailable for specific countries or regions via routine sources

OTHER GUIDANCE

- No relevant guidance identified

CURRENT TREATMENT OPTIONS

Treatment for AMN is symptomatic. An annual or bi-annual evaluation by a neurologist for treatment of spasticity and neuropathic pain and referral to an urologist are recommended. Plasma testosterone, cortisol, mineralocorticoids, ACTH levels and ACTH stimulation responses must be tested regularly and replacement therapy may be required. In adult males with AMN, a yearly brain MRI must be performed to detect early signs of cerebral demyelination and propose allogeneic hematopoietic stem cell transplantation if a donor is available.[7] Lorenzo's oil is currently under investigation as a treatment for AMN.[6] This is a 4:1 mixture of glyceryl trioleate and glyceryl trierucate, which when given orally and combined with a diet reduction of very long-chain fatty acids (VLCFA), has been shown to normalize the level of VLCFA in plasma. [2]

EFFICACY and SAFETY

Trial	NCT02961803, MD1003-AMN MD1003 in Adrenomyeloneuropathy; adults; High Dose biotin vs placebo; phase II/III
Sponsor	MedDay Pharmaceuticals SA
Status	Ongoing
Source of Information	Trial registry[3]
Location	3 EU countries not UK
Design	Randomised, placebo-controlled, double-blind study
Participants	n= 67, males, aged 18-60 years, ABCD1 gene mutation identified, elevated plasma VLCFA, clinical signs of AMN with at least pyramidal signs in the lower limbs and difficulties to walk Note: this is not an exhaustive list of the inclusion criteria
Schedule	The study lasts for 12 months followed by a 12 month extension phase during which all subjects are treated with MD1003.

	Subjects are randomized into two arms: Arm I - Subjects (n=40) receive MD1003 capsule at a dose of 100 mg orally, 1 capsule three times a day for 24 months Arm II - Subjects (n=20) receive placebo capsule orally, 1 capsule three times a day for 12 months, then switch to MD1003 100mg capsule, 1 capsule three times a day for 12 months
Follow-up	12 months
Primary Outcomes	Mean change of 2-Minutes-Walk-Test (2MWT) between months 12 and baseline [Time Frame: Baseline and 12 Months]
Secondary Outcomes	Proportion of patients with improved 2MWT of at least 20% [Time Frame: Baseline, 9 months, 12 months] at months 9 and months 12 compared to the best value among screening and baseline Proportion of patients with improved TW25 (time to walk 25 feet) of at least 20% [Time Frame: Baseline, 9 months, 12 months] at months 9 and months 12 compared to the best value among screening and baseline Mean Change in TW25 [Time Frame: Baseline and 12 months] Timed Up and Go test [Time Frame: 12 Months] Euroqol EQ-5D questionnaire [Time Frame: 12 months] Quality of Life questionnaire Qualiveen Questionnaire [Time Frame: 12 Months] Qualiveen to evaluate urinary function
Key Results	-
Adverse effects (AEs)	-
Expected reporting date	Study completion date reported as August 2017.

ESTIMATED COST and IMPACT

COST

The cost of biotin is not yet known.

IMPACT – SPECULATIVE

IMPACT ON PATIENTS AND CARERS

☐ Reduced mortality/increased length of survival

☒ Reduced symptoms or disability

☒ Other: *specify, e.g. improved quality of life for carers, improved patient convenience, wider societal benefits (e.g. earlier return to normal activities, including employment) etc.*

☐ No impact identified

IMPACT ON HEALTH and SOCIAL CARE SERVICES

☐ Increased use of existing services

☒ Decreased use of existing services

☐ Re-organisation of existing services

☐ Need for new services

☐ Other: *specify, e.g. new staff training requirements, requirement for new facilities, specialist laboratory testing, etc.*

☐ None identified

IMPACT ON COSTS and OTHER RESOURCE USE

☒ Increased drug treatment costs

☐ Reduced drug treatment costs

☐ Other increase in costs: *specify, e.g. new specialist clinics required, capital investment required, additional staff training required, additional costs for IV administration in clinic, more patients eligible for treatment, etc.*

☐ Other reduction in costs: *specify, e.g. reduced use of secondary care/specialist services, reduced need for interventional procedures, reduced social care costs, etc.*

☐ Other: *specify, e.g. uncertain unit cost compared to existing treatments*

☐ None identified

OTHER ISSUES

☐ Clinical uncertainty or other research question identified: *specify*

☒ None identified

REFERENCES

[1] MedDay Pharmaceuticals. *Our Discovery Development Story*. Available from: http://www.medday-pharma.com/research-development/pipeline/md1003/ [Accessed 15th June 2017]

[2] MedDay Pharmaceuticals. *About adrenomyeloneuropathy*. Available from: http://www.medday-pharma.com/research-development/pipeline/md1003/adrenomyeloneuropathy/[Accessed 15th June 2017]

[3] ClinicalTrials.gov. *MD1003-AMN MD1003 in Adrenomyeloneuropathy*. Available from: www.clinicaltrials.gov/show/NCT02961803 [Accessed 15th June 2017]

[4] Global data. *Product Search - View Results*. Available from: https://pharma.globaldata.com/AdvancedProductsData.aspx [Accessed 15 June 2017, log-in required]

[5] Engelen M, Kemp S, De Visser M, van Geel BM, Wanders RJ, Aubourg P. X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet journal of rare diseases.* 2012 Aug 13;7(1):51.

[6] Genetic and Rare Disease Information Center. *Adrenomyeloneuropathy*. Available from https://rarediseases.info.nih.gov/diseases/10614/adrenomyeloneuropathy [Accessed 29 June 2017]

[7] ORPHANET. *Adrenomyeloneuropathy*. http://www.orpha.net/consor/cgi-bin/OC_Exp.php?Expert=139399 [Accessed 15th June 2017]

[8] NHS Digital. *Hospital Admitted Patient Care Activity, 2015-16*. Available from: http://www.content.digital.nhs.uk/catalogue/PUB22378 [Accessed 03 July 2017]