Azafaros Announces FDA Grant of Orphan Drug Designation for AZ-3102 in the Treatment of Niemann-Pick Disease

- Second Orphan Drug Designation Supports Azafaros' Strategy to Develop AZ-3102 as a Disease Modifying Treatment in a Range of Severe Rare Inherited Metabolic Disorders –

Leiden, The Netherlands, March 24, 2022 – Azafaros B.V. today announced that the US Food and Drug Administration (FDA) has granted Orphan Drug Designation (ODD) for AZ-3102, a novel small molecule with a unique dual mode of action, in Niemann-Pick disease type C (NP-C). The designation was based on promising preclinical data of AZ-3120 in a NP-C mouse model, recently presented at the 18th Annual WORLD*Symposium™*. AZ-3102, Azafaros' lead program, is currently in clinical development as a potential treatment for the rare lysosomal storage diseases GM1 and GM2 Gangliosidoses and has completed a successful first-in-human clinical study in healthy subjects showing positive safety, tolerability, and pharmacodynamics data. The compound already received ODD from the FDA for GM2 Gangliosidosis including both Sandhoff and Tay-Sachs diseases. Based on its mode of action, AZ-3102 has broad applicability in addressing these inherited metabolic disorders.

"As we explore the broad potential of AZ-3102 as a promising new treatment option for rare disease patients, we are excited to achieve this further validation from the FDA," said **Stefano Portolano, Chief Executive Officer of Azafaros**. *"Our orally available azasugar is designed to selectively inhibit two enzymes involved in glycolipid metabolism with the goal of reducing toxic glycolipid accumulation and ameliorate impaired lysosomal function. We appreciate this acknowledgement of our mechanism of action and the urgency to support the rare inherited metabolic disorder patient community with safe and effective therapies."*

NP-C is caused by mutations in the NPC1 gene (NPC type 1C) or the NPC2 gene (NPC type 2C) and is inherited in an autosomal recessive manner. NP-C is a fatal genetic lysosomal storage disorder due to the abnormal function of proteins which regulate the transport of cholesterol from the lysosome to cytoplasm of the cells in numerous organs, including the liver, the spleen, the lungs and the brain. In the brain, the intracellular accumulation of cholesterol contributes to the accumulation of glycosphingolipids, similar to GM2 Gangliosidosis.

The preclinical data supporting the grant of the ODD showed sustained exposure of AZ-3102 and evident pharmacodynamic effect. In addition, in the animal group treated with AZ-3102, tremor levels were reduced, and cerebellar Purkinje cells, which are normally depleted in untreated NP-C animals, were significantly spared.

Orphan Drug Designation by the US FDA provides drug developers with special status and incentives to facilitate the development of therapeutics for rare diseases affecting fewer than 200,000 people in the US. The designation provides seven years of market exclusivity if the drug candidate receives regulatory approval together with exemptions from certain FDA application fees, advice on clinical trial design and tax credits for qualified clinical trial costs.

About AZ-3102

Azafaros' proprietary clinical azasugar, AZ-3102, is an orally available, small molecule designed to be a potent and selective inhibitor of two target enzymes involved in glycolipid metabolism, originally based on discoveries[1] from Leiden University and Amsterdam University Medical Center. It is designed to

selectively inhibit two enzymes involved in glycolipid metabolism, called glucosylceramide synthase (GCS) and non-lysosomal neutral glucosylceramidase (GbA2). This dual mode of action aims to reduce toxic glycolipid accumulation. Azafaros completed a first-in-human clinical trial with AZ-3102 in healthy volunteers in 2021 and received Orphan Drug Designation in GM2 Gangliosidosis from the FDA in February 2022.

About Azafaros

Founded in 2018 with a deep understanding of rare genetic disease mechanisms and led by a team of highly experienced industry experts, Azafaros aims to build a pipeline of disease-modifying therapeutics to offer patients and their families new treatment options. The company's lead clinical-staged program is AZ-3102, a highly differentiated, orally available, small molecule with the potential to treat GM1 and GM2 Gangliosidoses and other metabolic disorders. By applying its know-how, network, and courage, the Azafaros team challenges traditional development pathways to rapidly bring new drugs to the rare disease patients who need them. Azafaros is supported by a syndicate of leading Dutch and Swiss investors including Forbion, BioGeneration Ventures, BioMedPartners and Schroder Adveq.

For further information:
Azafaros B.V.
Email: info@azafaros.com
www.azafaros.com

For media inquiries:
Trophic Communications
Eva Mulder and Marie-Theresa Weickert
Email: azafaros@trophic.eu
Phone: +49 (0) 175 222 57 56

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[1] Ghisadoobe et al., 2014, J Med Chem, doi: 10.1021/jm501181z