Azafaros Presents Positive Clinical and Preclinical Data Supporting Development of Lead Compound AZ-3102 in Lysosomal Storage Disorders at the 18th Annual WORLD*Symposium*™ Conference

- Positive Safety, Tolerability and Pharmacodynamics Data from Multiple Dose Levels in Healthy Volunteers Support Evaluation of AZ-3102 in GM1 and GM2 Gangliosidoses -

- Two Preclinical *in Vivo* Studies with AZ-3102 Elucidate Potential as a Treatment for Sandhoff and Niemann-Pick Type C Diseases -

- Presentation of Design for PRONTO Natural History Study in GM1 and GM2 Gangliosidoses Patients -

Leiden, The Netherlands, February 14, 2022 – Azafaros B.V. announced positive clinical data from its first-in-human Phase 1 study with AZ-3102, the company's lead program in development as a potential treatment for pediatric neurogenetic lysosomal storage disorders (LSDs). AZ-3102 is an azasugar, orally available, small molecule designed to be a potent and selective inhibitor of two target enzymes involved in glycolipid metabolism by modulating the metabolism of glycosphingolipids. Azafaros also presented the design of PRONTO, a prospective longitudinal global study of neurological disease trajectory in children living with late-infantile or juvenile onset of GM1 or GM2 Gangliosidoses.

In two plenary oral presentations, the company detailed strong preclinical *in vivo* data for AZ-3102 in Sandhoff and Niemann-Pick Type C (NPC) mouse models. All four presentations were made at the 18th Annual WORLD*Symposium*™, held February 7 – 11, 2022, in San Diego, CA.

Data from the Phase 1 study with AZ-3102 in healthy volunteers demonstrate its positive safety and tolerability profile and provide the first clinical proof of the compound's mechanism of action. AZ-3102 is designed to selectively inhibit two enzymes involved in glycosphingolipid metabolism, called glucosylceramide synthase (GCS) and non-lysosomal glucosylceramidase (GbA2). This dual mode of action aims to counteract toxic glycolipid accumulation and ameliorate impaired lysosomal functions, two key factors driving the neuromotor defects caused by a range of LSDs.

Stefano Portolano, Chief Executive Officer of Azafaros, stated, *"The presentations at this year's WORLDSymposium™ conference demonstrate the exciting potential of AZ-3102 in rare metabolic diseases. I am proud of the skillset and commitment of the Azafaros team who in just over 3 years have navigated the development of this compound from the discovery stage to sharing positive first-in-human data at this important conference. These data support development of AZ-3102 as a potential disease modifying treatment option for children living with GM1 and GM2 Gangliosidoses, two severe, highly debilitating, and life-threatening neurological diseases with dismal prognosis. We will build on the momentum of AZ-3102's development and plan to initiate a pivotal Phase 2 study in the second half of 2022."*

The results from the randomized, double-blind, placebo controlled, two-part Phase 1 clinical study in 35 healthy volunteers demonstrated that daily oral treatment with AZ-3102 was safe and well-tolerated at all dose levels tested. The gastrointestinal tolerability was very benign, with no episodes of diarrhea. Pharmacokinetics after single and multiple doses was fully in line with expectations from animal pharmacology data. Multiple doses of AZ-3102 demonstrated a marked and sustained reduction of blood level glycolipids. Additionally, levels of glucosylceramide (GlcCer) showed several folds of increase in the cerebrospinal fluid (CSF) consistent with AZ-3102's expected

pharmacodynamics. The results show strong target engagement in both the blood and brain, underscoring AZ-3102's unique and selective dual mode of action and supporting clinical development of AZ-3102 in GM1 and GM2 Gangliosidoses.

Kyle Landskroner, Head of Preclinical Drug Development at Azafaros, added, *"Our new preclinical data with AZ-3102 strongly supports our development strategy in GM1 and GM2 Gangliosidoses and opens the avenue to investigate AZ-3102 as a potential treatment for Niemann-Pick Type C disease (NPC). For our lead indication, the Sandhoff mouse model demonstrated that treatment with AZ-3102 effectively results in improved survival; our preclinical data in an NPC mouse model demonstrated a significant reduction in Purkinje cell death, a prominent feature of the neuropathology of this disease."*

The preclinical study conducted in a Sandhoff disease mouse model showed that treatment with AZ-3102 is associated with significantly extended survival, in addition to compelling improvements in behavioural assessments of activity. In the NPC mouse model, there was sustained exposure of AZ-3102 and increased GlcCer levels in the brain, consistent with AZ-3102's evident pharmacodynamic effect. Moreover, AZ-3102 reduced tremor levels and significantly spared cerebellar Purkinje cells, which are normally depleted in untreated NPC animals.

The company also presented the design of the PRONTO study, a prospective global study aimed to longitudinally characterize neurological disease trajectory in children living with late, infantile or juvenile onset of GM1 or GM2 Gangliosidosis. Longitudinal data on the progression of neurological manifestations in these patient populations are sparse, scarce, and not homogeneously collected. In the new study, standardized neurological assessments, including but not limited to the rating of cerebellar ataxic manifestations, will be applied consistently throughout all study sites. The study is planned to be conducted in 6 countries and aims at recruiting 75 patients who will be followed for up to 48 months. The majority of the visits will be done virtually in a high-technology setting. The primary outcome measure is based on the Scale for Assessment and Rating of Ataxia (SARA), a validated tool to measure gait and posture, speech articulation and kinetic function of the limbs.

All four of the presentations delivered at the 18th Annual WORLDSymposium™ can be accessed through the News and Events section on the Azafaros website.

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.

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