Press Release
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BioSenic publishes new data on the mechanism of action of arsenic trioxide (ATO)

Combination of ATO with copper salts will allow BioSenic to work towards reducing the dosage of ATO in future trials overall and maintain efficacy

Mont-Saint-Guibert, Belgium, March 30, 2023 – BIOSENIC (Euronext Brussels and Paris: BIOS), the clinical stage company specializing in severe autoimmune/inflammatory diseases and cellular repair, today announces that data providing additional details about the mechanism of action of its lead API arsenic trioxide (ATO) to prevent autoimmune diseases has now been published in a peer-reviewed paper. The article entitled *"Optimal combination of arsenic trioxide and copper ions to prevent autoimmunity in a murine HOCl-induced model of systemic sclerosis"* also details an original ATO formula to maximize efficacy in fighting autoimmunity and reducing side effects. The peer-reviewed paper is published in *Frontiers in Immunology***.** This new formulation data has been completed following pre-clinical activities and does not constitute data validated through clinical trial.

BioSenic has already demonstrated safety and efficacy of arsenic trioxide in clinical programs targeting Chronic Graft-versus-Host Disease (cGvHD), with a successful Phase 2 trial and a Phase 2a trial on systemic lupus erythematosus (SLE). BioSenic considers that the clinical data it has generated during the last two decades will be adequate for its trial submissions of new indications in the field of autoimmunity and inflammatory diseases.

"BioSenic is making further significant progress in elucidating the fundamental mechanism of action of arsenic trioxide. Our company is in the process of further understanding the efficacy of arsenic trioxide in the treatment of various autoimmune diseases, where the pleiotropic effects of arsenic trioxide may contribute to significantly controlling and restoring a normal functioning immune system. This involves using ATO to manage the effects on the oxidative stress status of activated immune cells, on their ability to regulate the release of several pro-inflammatory cytokines or chemokines, or even on modulating the intensity of induction of inflammatory pathways, by directly interfering with regulatory proteins. This is done in order to get a better understanding on the way to positively interact with the pathophysiological, harmful mechanisms leading to chronic pathology in various autoimmune conditions. BioSenic has a number of forthcoming milestones across its clinical pipeline. This includes the launch of a Phase 3 trial in Chronic Graft-versus-Host Disease this year and a Phase 2b trial being prepared for systemic lupus erythematosus later on," said Francois Rieger, PhD, BioSenic's Chairman and CEO. *"The publication of this new peer-reviewed paper details the mechanism of action of ATO combined with copper salts as well as an ideal formulation to maintain efficacy while reducing ATO side effects. This will be critical for further ATO clinical development, including a Phase 2b trial in systemic sclerosis, which is a rare chronic autoimmune disease with no significant therapeutic option. We look forward to a fast delivery of new clinical results on all these conditions for the market, our investors, and chronically ill patients."*

The new peer-reviewed article also demonstrates that the efficacy of ATO is partly related to the generation of Reactive Oxygen Species (ROS), with a marked activation of oxidative cell phenomena and the ensuing selective deletion of activated -pathogenic- immune cells and fibroblasts. They improved the basic API's efficacy by combining ATO with copper (Cu2+), a divalent cation, which has Fenton-like properties, explaining its capacity to increase oxidative cell stress. BioSenic combines ATO with copper chloride since they both cooperate to trigger the production of ROS. As a result, 50 percent less ATO is needed in combination with copper to observe the same efficacy as ATO alone to treat experimental SSc in a pre-clinical model.

BioSenic's CSO, Dr Carole Nicco, has had a decisive input in the understanding of the mechanism of action of arsenic trioxide, making a significant contribution to this paper and another published in *Frontiers in Immunology* in 2022 "A Fenton-like cation can improve arsenic trioxide treatment of sclerodermatous chronic Graft-versus-Host Disease in mice". Biosenic's work in this part of its pipeline is now oriented towards gaining further evidence for using the combination of ATO with copper salts to treat auto-immune diseases and other conditions. She also contributed to the first two papers along these lines, on cGvHD and SSc, as previously described by Kavian et al. (J Immunol 2012 May; Arthritis Rheum 2012 Oct).

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About BioSenic
BioSenic is a biotech company focused on (i) the development of innovative products to address high unmet needs in orthopedics and (ii) exploiting the possibilities offered by the therapeutic use of arsenic salts (mainly arsenic trioxide (ATO)) for patients with autoimmune diseases. Key target indications for the platforms include Graft versus Host Disease (GvHD), Systemic lupus erythematosus (SLE), Systemic Sclerosis (SSc) and high-risk tibial fractures. Following the merger in October 2022, BioSenic combines the strategic positionings an found d strengths of Medsenic and Bone Therapeutics. The merger also enables Biosenic to add to its innovative cell therapy platform and strong IP for tissue repair protection with an entirely new arsenal of various anti-inflammatory and anti-autoimmune formulations using theimmunomodulatory properties of ATO/OATO. BioSenic is based in the Louvain-la-Neuve Science Park in Mont-Saint-Guibert, Belgium. Further information is available at http://www.biosenic.com.

About BioSenic technology platforms
BioSenic's technology is based on:
1) The allogeneic cell and gene therapy platform, developed by BioSenic with differentiated bone marrow sourced Mesenchymal Stromal Cells (MSCs) that can be stored at the point of use in hospitals. Its current investigational medicinal product, ALLOB, represents a unique, proprietary approach to organ repair and specifically to bone regeneration, by turning undifferentiated stromal cells from healthy donors into bone-forming cells on the site of injury after a single local injection. These cells are produced via a BioSenic's scalable manufacturing process. Following the CTA approval by regulatory authorities in Europe, BioSenic has initiated patient recruitment for the Phase IIb clinical trial with ALLOB in patients with difficult tibial fractures, using its optimized production process. ALLOB is currently being evaluated in a randomized, double-blind, placebo-controlled Phase IIb study in patients with high-risk tibial fractures, using its optimized production process, after a successful first safety and efficacy study (Phase 1/2a) on fractured long bones, with late delayed union.
2) The Arsenic TriOxide (ATO) platform developed by Medsenic. The immunomodulatory properties of ATO have demonstrated a double basic effect on cells of the immune system. The first effect is the increase of the cell oxidative stress in activated B, T or other cells of the innate/adaptative immune system to the point they will enter a cell death program (apoptosis) and be eliminated. The second effect is potent immunomodulatory properties on several pro-inflammatory cytokines involved in inflammatory or autoimmune cell pathways. One direct application is its use in onco-immunology to treat GvHD (Graft-versus-Host Disease) in its chronic, established stage. GvHD is one of the most common and clinically significant complications affecting long-term survival of allogeneic hematopoietic stem cell transplantation (allo-SCT). GvHD is primarily mediated by the transplanted immune system that can lead to severe multiorgan damage. Medsenic had been successful in a phase II trial with its intravenous formulation, allowing arsenic trioxide to be granted an orphan drug designation status by FDA and EMA and is heading towards an international Phase III confirmatory study, with a new, IP protected, oral (OATO) formulation. Moderate to Severe forms of Systemic Lupus erythematosus (SLE) is another selected target, using the same oral formulation. ATO has shown good safety and significant clinical efficacy on several affected organs (skin, mucosae and the gastro-intestinal tract) in a phase IIa study. Systemic Sclerosis is, in addition, part of the clinical pipeline of BioSenic. Preclinical studies on pertinent animal models are positive. This gives good grounds to launch a phase II clinical protocol for this serious disease that badly affects skin, lungs or vascularization, and with no actual current effective treatment.

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