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ICHNOS SCIENCES INC.

AUGUST 2023 UPDATE

ABOUT ICHNOS

Ichnos Sciences aims to shift the way the world thinks about innovation in medicine by developing potentially transformative biologic treatments in immuno-oncology. The company, currently a subsidiary of Glenmark Holding, SA, plans to pursue external financing following achievement of clinical proof of concept for its lead assets.

Headquartered in New York City, Ichnos has research and manufacturing operations at two sites in Switzerland. As a fully integrated biotechnology company with approximately 164 employees following the recent restructuring of the Research group, Ichnos has strong capabilities in research, antibody engineering, CMC, and clinical development of biotechnologies.

Ichnos is guided by an accomplished management team with experience developing immune cell engagers within the biopharmaceuticals industry, and is led by Cyril Konto, M.D., President and Chief Executive Officer.

In June 2023, Ichnos welcomed Lida Pacaud, M.D. as the company's new Chief Medical Officer.

CYRIL KONTO, M.D. President and Chief Executive Officer Allogene, Pfizer, Bristol Myers Squibb	**LIDA PACAUD, M.D.** Chief Medical Officer Legend Biotech, Novartis, Roche	**EUGENE ZHUKOVSKY, Ph.D.** Chief Scientific Officer Genentech, Xencor, Affimed, Biomunex, Boehringer Ingelheim
MICHAEL D. PRICE Chief Financial Officer AKCEA, novelion	**ROBERTO GIOVANNINI, Ph.D.** Chief Process and Manufacturing Officer Boehringer Ingelheim, Glenmark	**ASHOK MARÍN** General Counsel sanofi, Gilead
PATRICIA JAQUET Head of Human Resources COVANCE		

The proprietary BEAT® technology platform[1] is the basis for Ichnos' clinical-stage oncology pipeline. Using this technology, coupled with the proprietary common light chain library, the company is developing novel multispecific immune cell engagers and modulators, with the goal of realizing its mission to provide breakthrough, potentially curative therapies that may extend and improve lives, writing a new chapter in healthcare.

ONCOLOGY PIPELINE

The first wave of Ichnos' multispecific antibody pipeline consists of five programs targeting a range of hematologic malignancies and solid tumor indications through engagement of a broad spectrum of immune cells. The most advanced programs are ISB 1342, a clinical-stage, potentially first-in-class bispecific antibody targeting CD38 and CD3, which is in Phase 1 for the treatment of relapsed/refractory multiple myeloma, and ISB 1442, a biparatopic bispecific antibody targeting CD38 and CD47, currently in a Phase 1/2 dose escalation/expansion study for the same indication. In April 2023, Ichnos received approval from the Human Research Ethics Commission (HREC) in Australia and the U.S. Food and Drug Administration (FDA) to initiate a first-in-human clinical study of ISB 2001, the company's first TREAT™ trispecific antibody targeting BCMA, CD38, and CD3, for the treatment of relapsed/refractory multiple myeloma. In July 2023, Ichnos was granted Orphan Drug Designation by the FDA for ISB 2001 for the treatment of multiple myeloma. Additionally, Ichnos selected targets for ISB 2301, the company's first NK-cell engaging mutlispecific platform, for the treatment of solid tumors.

Ichnos is looking for asset-level and platform-level collaboration partners in development and research. For more information, email us at Partnership@IchnosSciences.com.

[1] Bispecific Engagement by Antibodies based on the TCR

MOLECULE MECHANISM/CLASS	PHASE/STATUS	LEAD INDICATION
ISB 1342 CD38 x CD3 BEAT® bispecific antibody[2]	Phase 1	Relapsed/Refractory Multiple Myeloma; T-Cell Acute Lymphoblastic Leukemia(T-ALL) is also under consideration
ISB 1442 CD38 x CD47 BEAT® bispecific antibody	Phase 1	Relapsed/Refractory Multiple Myeloma; Phase 1 study in Acute Myeloid Leukemia (AML) is planned by early 2024
ISB 2001 BCMA x CD38 x CD3 TREAT™ trispecific antibody[3]	Phase 1	Relapsed/Refractory Multiple Myeloma
ISB 2004 BEAT® bispecific antibody	Discovery	Hematologic Malignancies
ISB 2301 NK-cell engaging multispecific platform	Discovery	Solid Tumors

OVERVIEW OF SELECT ONCOLOGY DRUG PRODUCT CANDIDATES

ISB 1342 (CD38 X CD3 BEAT® BISPECIFIC ANTIBODY)

- A Phase 1, open-label, dose-escalation, first-in-human study of ISB 1342 in patients with relapsed/refractory multiple myeloma is ongoing.
  - + Enrollment of patients receiving a weekly dosing regimen is ongoing.
  - + Number of sites participating in the study was expanded at the end of calendar year 2021 to enhance enrollment. Currently seven (7) sites in the US and eleven (11) sites in France are actively enrolling.
  - + The first partial response in this study was observed in Cohort 109 intravenous (dose level 8 µg/kg) and Cohort 110 intravenous (dose level 16 µg/kg) is now enrolling. In parallel, a new lyophilized formulation was filed and is now used in a subcutaneous dose-escalation arm, which is at Cohort 109 (dose level 8 µg/kg). Clinical proof of concept is anticipated in the third quarter of calendar year 2023.

[2] Future clinical development will be advanced by a partner
[3] Trispecific Engagement by Antibodies based on the TCR

- The primary objectives of the study are to:
  - Determine maximum tolerated dose and/or recommended Phase 2 dose of ISB 1342 (Part 1 dose escalation).
  - Assess anti-myeloma activity of ISB 1342 according to the International Myeloma Working Group response criteria (Part 2 dose expansion).
- Clinical safety remains on par with earlier results presented in a poster session at the 2022 American Society of Hematology (ASH) Annual Meeting in December (link) with data cut-off October 26, 2022:
  - Observed CRS events were moderate and manageable with supportive care
  - No increased risk of infection has been observed
  - Proof-of-Mechanism with evidence of T-cell activation was noted following treatment with ISB 1342
  - Dose escalation continues with participants enrolling in additional cohorts two parallel dose escalations IV and SQ
- ISB 1342 was granted Orphan Drug Designation for multiple myeloma by the U.S. Food and Drug Administration.
- The bulk drug substance is manufactured at the Ichnos site in La Chaux-de-Fonds, Switzerland.
- In July 2023, a research article, Preclinical characterization of ISB 1342, a CD38 × CD3 T-cell engager for relapsed/refractory multiple myeloma, was published in Volume 142, Issue 3, of the American Society of Hematology's *Blood* journal.
  - One of the figures from this publication was prominently featured on the cover of the print edition of the journal.
- An abstract for the 2023 ASH Annual Meeting with the latest clinical data has been submitted:
  - **Dose Escalation of ISB 1342, a Novel CD38xCD3 Bispecific Antibody, in Patients with Relapsed / Refractory Multiple Myeloma (RRMM)**

ISB 1442 (CD38 X CD47 BEAT® BISPECIFIC ANTIBODY)

- This first-in-class biparatopic bispecific antibody targeting CD38 and CD47 was generated by scientists in Ichnos' laboratories in Lausanne at the Biopole life sciences campus.
- ISB 1442 is designed to kill CD38-expressing tumor cells through inhibition of the CD47-

SIRPα axis to increase antibody-dependent cellular phagocytosis (ADCP) and enhance antibody-dependent cellular cytotoxicity (ADCC) as well as complement-dependent cytotoxicity (CDC).

- After receiving approval from the HREC in Australia and the U.S. Food and Drug Administration, a Phase 1/2 first-in-human dose-finding study of ISB 1442 in relapsed/refractory multiple myeloma is now actively enrolling patients in Cohort 4 in both countries.
- Currently four (4) sites in the US and four (4) sites in Australia are actively enrolling. The study is in cohort 4 (dose level 150mg).
- Ichnos also plans to develop ISB 1442 in acute myeloid leukemia (AML).
- The preclinical data package for ISB 1442, which may be viewed at this link, shows:
    + Higher potency in vitro for ISB 1442 relative to daratumumab in CD38 high/low tumor models as measured by a multiple antibody-dependent mechanisms of action killing assay
    + Higher tumor growth inhibition for ISB 1442 than daratumumab in CD38 high and low preclinical in vivo xenograft models
    + Low on-target off-tumor binding with ISB 1442 compared to anti-CD47 mAb (hu5F9), is anticipated to result in lower red blood cell depletion in clinic, and potentially a better therapeutic index than anti-CD47 bivalent monoclonal antibodies
- Additional information on the ongoing Phase 1 study and on preclinical models in other hematologic malignancies were most recently presented at the 2022 ASH Annual Meeting in December:
    + **A Phase 1/2, First-in-Human, Multicenter, Open-Label, Dose Escalation and Dose-Expansion Study of Single-Agent ISB 1442 in Patients with Relapsed/Refractory Multiple Myeloma**; Poster presentation that describes the design of the ongoing study may be viewed here (link).
    + **Preclinical Evaluation of ISB 1442, a First-in-Class CD38 and CD47 Bispecific Antibody Innate Cell Modulator for the Treatment of AML and T-ALL**; Poster presentation that shows the rationale for advancing to a clinical study in relapsed/refractory AML (link), specifically:
        - In AML cell lines in multiple *in vitro* assays, ISB 1442 induces killing, including ADCP and ADCC
        - Superior activity to daratumumab in AML cell lines having intermediate or low CD38 expression

- ISB 1442 was granted Orphan Drug Designation for multiple myeloma by the FDA in March 2023.
- The bulk drug substance is manufactured at the Ichnos site in La Chaux-de-Fonds, Switzerland.
- An abstract for the 2023 ASH Annual Meeting with the latest clinical data has been submitted:
    + **Initial Results from the Dose Escalation Phase1/2 of ISB 1442, a Novel CD38 Biparatopic x CD47 Bispecific Antibody, in Patients with Relapsed / Refractory Multiple Myeloma (RRMM)**

ISB 2001 TREAT™ TRISPECIFIC ANTIBODY

- ISB 2001 is the first-in-class T cell-engaging antibody that targets BCMA and CD38 on multiple myeloma cells. It is a trispecific antibody based on Ichnos' proprietary BEAT® platform, allowing maximal flexibility and excellent manufacturability of full-length multispecific antibodies. Additional ISB 2001 details include:
    + ISB 2001 combines three proprietary Fab antigen-binding arms, each targeting a different antigen, with one arm binding to the epsilon chain of CD3 on T cells, and the other two binding BCMA and CD38 on multiple myeloma cells. Its Fc domain was fully silenced to suppress Fc effector functions.
    + In vitro studies showed that ISB 2001 exhibited increased killing potency of tumor cells compared to all tested antibodies that are either currently approved for the treatment of multiple myeloma or are being tested in ongoing clinical studies. In vivo studies in the multiple myeloma models also demonstrated superior potency of ISB 2001 relative to approved antibody treatments of multiple myeloma.
    + ISB 2001 redirects CD3+ T lymphocytes to kill tumor cells expressing low to high levels of both BCMA and CD38. With two different tumor-associated antigens instead of one, ISB 2001 is expected to be more resistant to antigen escape associated with treatment of multiple myeloma patients.
- The preclinical data package for ISB 2001 was selected for a presentation (link) at the 2023 American Association for Cancer Research (AACR) Annual Meeting in April, as well as an oral presentation at the ASH Annual Meeting in December 2022 :
    + In this presentation, **Overcoming Mechanisms of Escape from Treatments for Multiple Myeloma by ISB 2001, a first-in-Class Trispecific BCMA and CD38 targeted T Cell Engager,** the following data were highlighted:
        - Increased killing of tumor cells across variable levels of expression of both BCMA and CD38 compared to teclistamab, alnuctamab and EM-801

  - Higher potency *in vitro* when compared to the combination of daratumumab and teclistamab

  - Superior cytotoxicity over teclistamab in *ex vivo* assays with Multiple Myeloma cells from patients at different stages of progression of the disease

  - Superior efficacy over teclistamab in *in vivo* models with low level of expression of CD38 and BCMA demonstrating 100% complete responses

- ISB 2001 received approvals from HREC in Australia and the FDA to initiate a Phase 1 first-in-human study of ISB 2001 for the treatment of relapsed/refractory multiple myeloma. Ichnos is considering expansion of clinical studies to additional countries in parallel.

- In July 2023, Ichnos received Orphan Drug Designation from the FDA for ISB 2001 for the treatment of multiple myeloma.

- The bulk drug substance is manufactured at the Ichnos site in La Chaux-de-Fonds, Switzerland.

- Two abstracts for the 2023 ASH Annual Meeting have been submitted. One describing the use of quantitative systems pharmacology (QSP) for determining the first in human (FIH) starting dose and the second one the trial design and specific mechanism of action:

  + **Integrated Preclinical data analysis of ISB 2001 enables optimal starting dose selection for a first in class trispecific T cell engager**

  + **A Phase 1, First-in-Human, Dose Escalation and Dose-Expansion Study of a BCMAxCD38xCD3 Targeting Trispecific Antibody ISB 2001 in Subjects with Relapsed/Refractory Multiple Myeloma**

AUTOIMMUNE DISEASES

Ichnos has two monoclonal antibody drug product candidates addressing autoimmune diseases in the pipeline. In order to enhance the company's focus on oncology, future development of both assets will be overseen by out-licensing partners.

The first asset, ISB 880, an anti-IL-1RAP antagonist, was licensed to Almirall, S.A. in December 2021. The initiation of dosing in a Phase 1 study of ISB 880/ALM27134 was announced by Almirall in September 2022. The second antibody, ISB 830 (telazorlimab), an OX40 antagonist that completed a Phase 2b study in moderate to severe atopic dermatitis in calendar year 2021, is in partnering discussions. Both compounds have potential across a range of autoimmune diseases.

ASSETS IN AUTOIMMUNE DISEASES

MOLECULE MECHANISM/CLASS	POTENTIAL INDICATIONS	PHASE	STATUS
ISB 880 (ALM 27134) IL-1RAP Antagonist Monoclonal Antibody	Autoimmune Diseases	Phase 1	Licensed to Almirall S.A. in December 2021. Dosing of participants in the Phase 1 study was announced by Almirall in September 2022.
ISB 830 Telazorlimab OX40 Antagonist Antibody	Atopic Dermatitis	Phase 2b	Successfully completed a Phase 2b study in Atopic Dermatitis. Exploring partnership(s).
	Other autoimmune diseases, including Rheumatoid Arthritis	U.S. IND for Rheumatoid Arthritis and other autoimmune indications is active.	

ISB 880 (IL-1RAP ANTAGONIST) almirall

- Ichnos entered an exclusive global licensing agreement for ISB 880 in autoimmune diseases with Almirall in December 2021. Within the terms of the agreement, Almirall assumed full cost and responsibility for the global development and commercialization of the compound. Ichnos received an upfront payment of €20.8 million. The deal includes development and commercial milestone payments and tiered royalties based upon future global sales. As part of the agreement, Ichnos is also being paid to manufacture batches of ISB 880 to support early clinical studies to be sponsored by Almirall and realized revenue this year for drug supplies for the ongoing Phase 1 study.

- ISB 880, a fully-human, high-affinity, monoclonal antibody blocking IL-1RAP signaling, has completed IND-enabling studies for patients with autoimmune diseases. The optimal antibody profile, the strong *in vitro* and *in vivo* data package, as well as toxicology, CMC, and clinical pharmacology plans enabled U.S. IND filing by Almirall, and a Phase 1 study is underway.

- Blockade of IL-1RAP simultaneously abrogates multiple disease drivers among the

IL-1 family of proinflammatory cytokine receptors, including IL-1R, IL-33R, and IL-36R, differentiating ISB 880 from single cytokine blockade therapies. These cytokines have been implicated in numerous autoimmune conditions, opening opportunities for ISB 880 to be positioned across broad disease indications.

- Ichnos retains rights for antibodies acting on the IL-1RAP pathway for oncology indications.

ISB 830 (TELAZORLIMAB, OX40 ANTAGONIST)

- The database for the ISB 830-204 Phase 2b clinical study in atopic dermatitis was locked in October 2021, and the final results were posted on ClinicalTrials.gov. This study, which was conducted in the U.S., Canada, Germany, Czech Republic, and Poland, had a randomized, controlled, multicenter design and assessed three doses and two dosing schedules of telazorlimab versus placebo in adults with moderate-to-severe atopic dermatitis.
- Results from the double-blind portion of the study are summarized below:
    - **Efficacy:** The primary endpoint of the EASI score, % change from baseline to Week 16, was achieved for the two highest doses of telazorlimab tested (300 mg and 600 mg q 2 weeks) versus placebo.
    - **Safety:** Telazorlimab was well tolerated. The most commonly reported adverse events (>5%) were atopic dermatitis, nasopharyngitis, upper respiratory tract infection, and headache. One patient with pre-existing hypertension in the telazorlimab group died due to a presumed cardiovascular event during the treatment period. The investigator considered the death to be unrelated to the study drug.
- Ichnos has clearance from the FDA to study telazorlimab in seropositive autoimmune diseases (Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjogren's Syndrome, Multiple Sclerosis, Type I Diabetes Mellitus, Myasthenia Gravis), and is actively seeking a partner to further develop the drug in atopic dermatitis and other indications. For more information, email us at Partnership@IchnosSciences.com.