Management Discussion & Analysis for the Third Quarter of FY 2022-23

Glenmark operates its businesses through three separate entities

Glenmark Pharmaceuticals Ltd. (GPL)

Glenmark Life Sciences (GLS)
(82.84% API subsidiary)

Ichnos Sciences
(100% US based innovation subsidiary)

Each of these three entities operate independently with separate Management Teams and Board of Directors.

Revenue Figures for Glenmark Pharmaceuticals Ltd. (Consolidated)

(Rs. In Million)

	For the third quarter ended December 31			For the nine months ended December 31		
	FY 2022-23	FY 2021-22	Growth (%)	FY 2022-23	FY 2021-22	Growth (%)
India	10,745	10,069	6.7%	32,014	32,009	0.0%
North America	8,373	7,567	10.6%	22,534	22,988	-2.0%
Europe	4,932	3,807	29.5%	12,016	10,250	17.2%
Rest of the World[1]	6,541	5,348	22.3%	16,921	16,194	4.5%
API	3,756	3,032	23.9%	10,751	9,426	14.1%
Total	**34,347**	**29,823**	**15.2%**	**94,236**	**90,865**	**3.7%**
Other Revenue	291	1,911	-84.8%	1,928	1,992	-3.2%
Consolidated Revenue	**34,639**	**31,734**	**9.2%**	**96,164**	**92,858**	**3.6%**

1. Asia, Middle East and Africa, Russia + CIS, and Latin America
2. Average conversion rate in 9M FY 2022-23 considered as INR 79.58 / USD 1.00
   Average conversion rate in 9M FY 2021-22 considered as INR 74.15 / USD 1.00
   USD figures are only indicative

Review of operations for the quarter ended December 31, 2022

For the third quarter of FY23, Glenmark's consolidated revenues from operations was at Rs. 34,639 Mn (USD 422.6 Mn) as against Rs. 31,734 Mn (USD 424.2 Mn) in the corresponding quarter last year, recording growth of 9.2%.

For the nine months of FY23, Glenmark's consolidated revenue was at Rs. 96,164 Mn (USD 1,208 Mn) as against Rs. 92,858 Mn (USD 1,252 Mn), recording a year-on-year growth of 3.6%.

GLENMARK PHARMACEUTICALS LTD. (GPL)

GPL is primarily focused on building a global formulation business with Branded, Generics, and OTC segments in the therapy areas of Dermatology, Respiratory and Oncology. It also has strong regional/country-specific presence in other therapeutic areas like diabetes, cardiovascular and oral contraceptives.

India

Sales from the formulation business in India for the third quarter of FY23 was at Rs. 10,745 Mn (USD 130.7 Mn) as against Rs. 10,069 Mn (USD 134.4 Mn) in the previous corresponding quarter, recording growth of 6.7%. The India business contribution was at 31% of the total revenues in Q3 FY23 compared to 32% in Q3 FY22.

As per IQVIA Q3 FY23 data, Glenmark's India formulation business recorded growth of 11%. As per IQVIA MAT December 2022, Glenmark's India business is ranked 14th with a market share of 2.19%. During the quarter, Glenmark's India business significantly improved its market share in key therapeutic areas of Cardiac and Dermatology. As per IQVIA MAT December 2022, the Cardiac segment market share increased to 5.37% from 4.85% last year and the Dermatology segment market share increased to 8.15% from 8.05% last year. Glenmark's market share in other key therapy areas also remained strong; the Company's share in Respiratory market was 5.34% and Diabetes market was 2.38% respectively.

As per IQVIA MAT December 2022, the company was ranked 2nd in Dermatology segment, 3rd in Respiratory segment (ranked 2nd in Q3 FY23), 5th in Cardiac segment and 14th in Diabetes segment. The company continues to have 9 brands in the IPM Top 300 brands in the country on the basis of IQVIA MAT December 2022.

The company launched multiple new products during the quarter and continued to gain market share in

some of the key launches across segments. In Q3, Glenmark launched Fixed-Dose Combination (FDC) of Teneligliptin (20 mg) + Pioglitazone (15 mg) + Metformin (500mg/1000mg) SR under the brand name Zita®-PioMet, a novel and affordable FDC to help improve glycemic control among adults with high HbA1c and high insulin resistance, by also improving adherence with single pill. Earlier in FY23, Glenmark also launched Sitagliptin (Sitazit®) and its FDCs, followed by Lobeglitazone (LOBG®) and FDCs of Teneligliptin including its combinations with Pioglitazone (Zita Pio™) and Dapagliflozin (Zita-D™), emphasizing its focus on the Diabetes segment.

In the Cardiac segment, Glenmark recently launched Sacubitril + Valsartan under the brand name, Sacu V™ for the treatment of heart failure. The sacubitril-valsartan combination belongs to the class ARNI (Angiotensin receptor neprilysin inhibitor). This drug helps reduce the risk of cardiovascular related deaths and hospitalizations. The company continues to have a healthy pipeline of differentiated products which it plans to launch in the market going forward.

India – Glenmark Consumer Care (GCC) Business

Primary sales for GCC in Q3 FY23 was Rs. 431 Mn with growth of 16% mirrored by strong double digit secondary growth of 13%. For the nine months of FY23, GCC revenue stands at Rs. 1,634 Mn with YTD growth of 34%. Our flagship brand Candid Powder™ delivered revenue growth of 9% for Q3 FY23 and 38% for 9M FY23. La Shield™ portfolio delivered 36% growth in Q3 FY23 and 81% growth in 9M FY23. We have also expanded the La Shield product range through the launch of La Shield Moisturizer. Finally, Scalpe+™ portfolio recorded 12% growth in Q3 FY23 and 13% growth in 9M FY23.

North America

North America registered revenue from the sale of finished dosage formulations of Rs. 8,373 Mn (USD 102.3 Mn) for the third quarter of FY23 as against revenue of Rs. 7,533 Mn (USD 94.8 Mn) for the second quarter of FY23, recording a QoQ growth of 11%. North America business contributed 24% to the consolidated sales in Q3 FY23, compared to 22% in Q2 FY23.

In the third quarter of fiscal year 2022-23, Glenmark received final approval for Nicardipine Hydrochloride Capsules. Glenmark received final approval and launched Sodium Phenylbutyrate Tablets USP, 500 mg. In addition, Glenmark also launched Fingolimod Capsules, 0.5 mg and a new pack size for Olmesartan Medoxomil Tablets USP [5 mg, 90's]. Glenmark filed one ANDA in the third quarter and plans to file six-eight applications in the forthcoming quarter.

Further, in Q3 FY23, Glenmark reached a settlement agreement with Pfizer Inc., PF Prism C.V., and PF Prism

IMB B.V. (Pfizer) for Axitinib Tablets, 1 mg and 5 mg, the generic version of their Inlyta® Tablets, 1 mg and 5 mg. Glenmark had previously announced that it had received a tentative approval by the U.S. FDA for their generic Axitinib Tablets, 1 mg and 5 mg on November 30, 2020. According to IQVIA™ sales data for the 12-month period ending December 2022, the Inlyta® Tablets, 1 mg and 5 mg market achieved annual sales of approximately USD 657.1 Mn.

Glenmark's marketing portfolio through December 31, 2022 consists of 178 generic products authorized for distribution in the U.S. market. The Company currently has 46 applications pending in various stages of the approval process with the US FDA, of which 21 are Paragraph IV applications.

Europe

Glenmark Europe operations' revenue for the third quarter of FY23 was at Rs. 4,932 Mn (USD 60.5 Mn) as against Rs. 3,807 Mn (USD 50.9 Mn) recording a growth of 29.5%. Europe business contributed 14% to the total revenues in Q3 FY23 compared to 12% in Q3 FY22.

The strong European business growth was driven by markets in both regions of Western Europe (WEU) and Central & Eastern Europe (CEE). Key markets in CEE such as the Czech and Poland recorded strong secondary sales double digit growth during the quarter. Growth was driven by uptick in base business as well as new product launches in the CEE markets in Q3 FY23. Western European business clocked high double digit growth for Q3 with markets like the Netherlands, the United Kingdom & Germany all growing significantly. In the UK, the overall pharmaceutical market witnessed some supply disruptions which helped Glenmark gain additional share through continued supply to key customers. Six new products were launched in the WEU markets. The respiratory portfolio launched by Glenmark continues to do well in Europe. Key brands such as Ryaltris® and Salmex® / Asthmex® have gained market share, both in volume as well as in value across the CEE markets. Tiogiva® also continues to grow in the WEU markets.

ROW Region (Asia, MEA, LATAM and RCIS)

For the third quarter of FY23, revenue from the ROW region was Rs. 6,541 Mn (USD 80.1 Mn) as against Rs. 5,348 Mn (USD 71.4 Mn) for the previous corresponding quarter, recording a growth of 22.3%. ROW business contributed 19% to the total revenues in Q3 FY23 compared to 17% in Q3 FY22.

Glenmark' Russia business recorded secondary sales growth of 26% in value and 3% in units in Q3 FY23 (vs same period last year). Strong growth has been driven by all key brands, including Ryaltris, Montlezir™, Candiderm™ and Candibiotic™ drops. Ryaltris has been included into the Guidelines of Russian Rhinology Society. Dimetindene gel (Fenismart™) was launched in October 2022 and additional registration approval has been received for Dimetindene oral drops. These two launches will further boost the Dermatology

segment. As per IQVIA MAT December 2022 data, Glenmark's Russia business growth was 15.9% in value terms, in line with overall retail market growth of 14.9%. Volume sales were also in line with the overall Russia market volume growth. Amongst the Dermatology companies in Russia, Glenmark ranks 12th as per MAT December 2022. Amongst the companies present on the Expectorants market of Russia, Glenmark continues to maintain a strong position, ranking 2nd as per MAT December 2022.

Amongst the key markets in the Asia region, Malaysia and the Philippines continued to record double-digit secondary growth. Certain macroeconomic headwinds are slowly easing out in other key markets like Sri Lanka. However, Myanmar continues to have challenges related to currency depreciation. Dermatology and Respiratory are key therapy areas contributing to majority of overall sales from Asia for Glenmark. Ryaltris continues to hold ~15% market share in Australia. Glenmark's partner in South Korea, Yuhan launched Ryaltris in Q3 FY23; the product has shown strong pickup with 30%+ share in the combination market in a short time span.

The Middle East and Africa region recorded ~30% growth in secondary sales during the third quarter of FY23. Kenya market continued to be impacted by macroeconomic instability and currency devaluation, however Glenmark continued to achieve strong secondary sales growth in South Africa and Saudi Arabia. On the back of key launches, Glenmark continues to gain scale in other markets of the region, such as UAE, Uganda and Tanzania. The Company also signed multiple business development deals to further augment the business growth.

LATAM witnessed strong growth for the nine months of FY23. Respiratory therapy area remains the key contributor for Glenmark in the LATAM markets. Glenmark has high single-digit market share across the chronic respiratory products in Brazil and is ranked 5th in Brazil as per IQVIA MAT December 2022 in the covered market of the chronic respiratory segment. Glenmark is growing faster than covered market across all segments. Secondary sales growth has remained strong in Mexico, growing at 15% compared to market growth of 8% in terms of value as per IQVIA MAT December 2022.

Respiratory – Creating Global Scale

Following are the key business updates for Glenmark's global respiratory business in Q3 FY23:

Ryaltris

- As of the end of the third quarter, marketing applications for Ryaltris have been submitted in 58 countries across the world, while it is commercialized in 23 markets, including major markets like the US, Europe (UK and 10 markets across the EU), Australia, Russia, South Korea and South Africa.
- Glenmark's partner in the EU, Menarini, initiated the commercial launch in the Nordic countries

(Denmark, Finland, Sweden, Norway) and Germany in the third quarter, and intends to launch the product in additional European markets in Q4.

- Our partner in the US, Hikma has launched the product and Ryaltris is now stocked at all major wholesalers. Discussions are ongoing with insurance companies to further increase coverage.
- During the third quarter, Glenmark submitted marketing authorization applications for Ryaltris in Hong Kong and Morocco. Glenmark received MA grant for Ryaltris in Tanzania in December 2022 and is awaiting approval in key markets like Brazil, Mexico, Vietnam, etc.
- Glenmark's partner in Mainland China, Grand Pharmaceutical (China) Co. Ltd., aims to complete enrollment of the on-going Phase 3 study in China and submit the marketing authorization application by end of 2023.
- Glenmark intends to soon launch Ryaltris in Canada via its partner Bausch Health

Other key products

- Clinical trial ongoing for generic Flovent pMDI; Expect to file in CY23
- Plan to file at least one more generic respiratory pMDI in the US in CY23 and continue filing momentum beyond FY24

Innovative R&D Pipeline

GRC 54276

GRC 54276 (HPK1 Inhibitor) is being developed as an orally administered IO-adjuvant treatment for patients with solid tumors. Hematopoietic progenitor kinase 1 (HPK1), is a negative regulator of T and B cell receptor signaling and an attractive therapeutic strategy for immuno-oncology based treatment in cancers. GRC 54276 is a novel, orally active HPK1 inhibitor that demonstrates excellent stand-alone efficacy and enhances current immunotherapy efficacy. A Phase 1 dose escalation study is ongoing in India. Successful recruitment of patients in Cohort 3 was completed in Q3 FY23. No dose limiting toxicities have been observed till date. IND submission and DCGI submission is planned in Q4 FY23 to initiate the part 2, combination study of GRC 54276 with pembrolizumab and atezolizumab in the US and India.

GRC 39815

GRC 39815 (RORγt inhibitor) is the company's respiratory pipeline asset being developed as an inhaled therapy for treatment of mild to moderate Chronic Obstructive Pulmonary Disorder (COPD), currently under Phase 1 clinical development in the US.

GLENMARK LIFE SCIENCES LTD. (GLS)

Glenmark Life Sciences is focused on manufacturing and marketing of Active Pharmaceutical Ingredients (API) products across all major markets globally. It also includes captive sales (i.e. use of API by GPL for its own formulations).

Revenues from operations including captive sales were Rs. 5,407 Mn as against Rs. 5,225 Mn, recording a YoY growth of 3.5%. Generic API revenues in Q3 FY23 increased 5.9% QoQ and increased 1.8% YoY. Regulated markets business continues the strong growth momentum, with contribution increasing to 76.5%. CDMO revenues in Q3 FY23 decreased by 9.6% QoQ; demand is expected to pick up from Q4 FY23 onwards. DMF/CEPs filing continued across major markets in Q3 FY23, taking the total cumulative filings to 456 as on Dec 31, 2022. Multiple projects are completed / ongoing for capacity expansion across Ankleshwar and Dahej.

External sales for Glenmark Life Sciences in Q3 FY23 were at Rs. 3,756 Mn (USD 45.8 Mn) as against Rs. 3,032 Mn (USD 40.5 Mn) in Q3 FY22, recording a growth of 23.9% YoY.

For further updates on the organization, please log on to www.glenmarklifesciences.com.

ICHNOS SCIENCES Inc.

Glenmark has invested Rs. 1,518 Mn (USD 18.5 Mn) in the third quarter of FY23 compared to Rs 1,520 Mn (USD 20.5 Mn) in the corresponding quarter last year. For the first nine months of FY23, Glenmark has invested Rs. 4,880 Mn (USD 61.3 Mn) compared to Rs. 4,987 Mn (USD 67.5 Mn) invested in the corresponding period of the previous financial year.

For further updates on the pipeline and the organization, please log on to www.ichnossciences.com. The pipeline update for the third quarter of FY23 is published on the website.

KEY OBJECTIVES FOR FY23

- Revenue growth of 6-8% during the year
- Sustain EBITDA margin performance at similar levels of FY22
- Capex of Rs. 7-8 Bn
- Strategic priority to enhance free cash generation for further debt reduction
- Continue discussion with potential partners for out-licensing of innovative assets

Disclaimer

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ICHNOS SCIENCES INC.

FEBRUARY 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 225 employees, 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.

CYRIL KONTO, M.D. President and Chief Executive Officer Allogene, Pfizer, Bristol Myers Squibb	**ROBERTO GIOVANNINI, Ph.D.** Chief Process and Manufacturing Officer Boehringer Ingelheim, Glenmark	**PATRICIA JAQUET** Head of Human Resources COVANCE
GRACE MAGUIRE Head of Communications and Corporate Affairs Forest Laboratories, Inc., Wyeth	**ASHOK MARÍN** General Counsel sanofi, GILEAD	**MICHAEL D. PRICE** Chief Financial Officer AKCEA, novelion
EUGENE ZHUKOVSKY, Ph.D. Chief Scientific Officer AFFIMED, BIOMUNEX, xencor, Boehringer Ingelheim		

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.

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

MOLECULE MECHANISM/CLASS	PHASE/STATUS	LEAD INDICATION
ISB 1342 CD38 x CD3 BEAT® bispecific antibody*	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[2]	IND-Enabling Studies	Relapsed/Refractory Multiple Myeloma
ISB 2004 BEAT® bispecific antibody	Discovery	Hematologic Malignancies/ Solid Tumors
NK-cell engaging multispecific platform (formerly ISB 2005)	Discovery	Solid Tumors

**Future clinical development will be advanced by a partner*

[1] Bispecific Engagement by Antibodies based on the TCR
[2] Trispecific Engagement by Antibodies based on the TCR

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. New locations in the U.S. were added and 11 sites were opened for enrollment in France and are now recruiting subjects.
  - Clinical proof of concept in the ongoing study is anticipated in second quarter of calendar year 2023.
- 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 data on this ongoing Phase 1 study were presented in a poster session at the 2022 American Society of Hematology (ASH) Annual Meeting in December. A summary appears below, and the poster may be viewed here (link):
  - Initial Results (data cut-off October 26, 2022) of Dose Escalation of ISB 1342, a Novel CD3 x CD38 Bispecific Antibody, in Patients with Relapsed / Refractory Multiple Myeloma (RRMM)
    - Treatment with ISB 1342 was well tolerated at the evaluated Q1W dose levels up to cohort 108 (1 µg/kg priming, 4 µg/kg targeted dose)
    - Observed CRS events were moderate and manageable with supportive care
    - No increased risk of infection has been observed
    - Evidence of T-cell activation was noted following treatment with ISB 1342
    - Dose escalation continues with participants enrolling in additional cohorts
- ISB 1342 was granted Orphan Drug Designation for multiple myeloma by the FDA.
- The bulk drug substance is manufactured at the Ichnos site in La Chaux-de-Fonds, Switzerland.

ISB 1442 (CD38 X CD47 BEAT® BISPECIFIC ANTIBODY)

- This first-in-class biparatopic bispecific antibody targeting CD38 x 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).
- An IND was filed with the US Food and Drug Administration last year and a Phase 1/2 first-in-human dose-finding study of ISB 1442 in relapsed/refractory multiple myeloma began dosing patients in September 2022. 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 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

- The first bulk drug substance batches to support IND filing and the ongoing Phase 1/2 dose escalation and expansion study were manufactured at the Ichnos site in La Chaux-de-Fonds, Switzerland in 2021.

- An application for Orphan Drug Designation for ISB 1442 for the treatment of multiple myeloma was submitted to the FDA and is currently under review.

ISB 2001 TREAT™ TRISPECIFIC ANTIBODY

- ISB 2001 is the first 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 manufacturability of full-length multispecific antibodies. Additional ISB 2001 details include:

    + ISB 2001 combines three proprietary fragment 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 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 has increased binding specificity to multiple myeloma cells due to enhanced avidity-based binding and is also 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 oral presentation (link) at the 2022 ASH Annual Meeting in December:

    + In this presentation, **ISB 2001, a First-in-Class Trispecific BCMA and CD38 T Cell Engager Designed to Overcome Mechanisms of Escape from Treatments for Multiple Myeloma by Targeting Two Antigens,** 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 in patient bone marrow aspirates

- Currently in IND-enabling studies, Ichnos intends to file an Australian CTN and US IND for ISB 2001 in the first quarter of calendar year 2023 and is considering expansion of clinical studies to additional countries in parallel.
- The first bulk drug substance batches to support IND filing and the Phase 1 dose escalation and expansion study were manufactured at the Ichnos site in La Chaux-de-Fonds, Switzerland in 2022.

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. Initiation of dosing in a Phase 1 study of ISB 880 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)

- 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.
- To date, there is no IL-1RAP antagonist approved or under clinical development for autoimmune disease, positioning ISB 880 as a potential first-in-class therapeutic.
- 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.