Management Discussion & Analysis
for the Fourth Quarter of FY 2023-24

Revenue Figures for Continuing Operations of Glenmark Pharmaceuticals Ltd.

(In INR Million)

	For the fourth quarter ended March 31			For the twelve months ended March 31		
	FY 2023-24	FY 2022-23	Growth (%)	FY 2023-24	FY 2022-23	Growth (%)
India	9,391	8,316	12.9%	33,994	40,463	-16.0%
North America	7,557	8,628	-12.4%	30,943	31,481	-1.7%
Europe	6,118	6,078	0.7%	24,205	18,097	33.7%
Rest of the World[1]	7,528	6,864	9.7%	27,666	23,834	16.1%
Total	**30,594**	**29,886**	**2.4%**	**1,16,807**	**1,13,876**	**2.6%**
Other Revenue	36	119	-70.1%	1,324	1,957	-32.3%
Consolidated Revenue	**30,630**	**30,005**	**2.1%**	**1,18,131**	**1,15,832**	**2.0%**

1. Russia + CIS (RCIS), Latin America (LATAM), Middle East and Africa (MEA), Asia

Average conversion rate in 12M FY 2023-24 considered as INR 82.78 / USD 1.00

Average conversion rate in 12M FY 2022-23 considered as INR 80.22 / USD 1.00

USD figures are only indicative

Review of Operations for the Quarter ended March 31, 2024

For the fourth quarter of FY24, Glenmark's consolidated revenue from operations was at Rs. 30,630 Mn (USD 368.9 Mn) as against Rs. 30,005 Mn (USD 365.4 Mn) in the corresponding quarter last year, recording overall year-on-year (YoY) growth of 2.1%.

For the twelve months of FY24, Glenmark's consolidated revenue was at Rs. 1,18,131 Mn (USD 1,427.1 Mn) as against Rs. 1,15,832 Mn (USD 1,443.9 Mn), recording a YoY growth of 2.0%

Key highlights for the Fiscal Year 2024

- **In the fourth quarter, Glenmark gained 2 positions to be ranked as the 3rd largest company in the Cardiac segment of the Indian Pharmaceutical Market as per IQVIA March 2024**
- **Glenmark's Europe business registered a strong growth of 33.7% for the full year**
- **Glenmark's ROW business recorded a robust YoY growth of 16.1%, driven by all key markets**
- **RYALTRIS® was launched in additional 7 markets across the globe, either on our own or through a commercial partner. As of March 2024, RYALTRIS® has been launched in 34 markets across the world**
- **The Company further enhanced its global branded portfolio through the in-licensing of Envafolimab for India & ROW markets, and Winlevi® for select European markets, the UK and South Africa**
- **Ichnos Sciences announced the exclusive world-wide out-licensing agreement for its OX40 portfolio, including ISB 830, with Astria Therapeutics, Inc.**
- **Glenmark and Ichnos Sciences entered in to an alliance – Ichnos Glenmark Innovation (IGI) – to accelerate new drug development in cancer treatment**
- **Glenmark completed the divestment of 75% of its stake in Glenmark Life Sciences (GLS) to Nirma Ltd.**

FORMULATION BUSINESS

Global formulation business with Branded, Generics, and OTC segments in the therapy areas of Dermatology, Respiratory and Oncology, along with strong regional/country-specific presence in other therapeutic areas like Cardiac, Diabetes and Oral Contraceptives.

INDIA

Sales from the formulation business in India for the fourth quarter of FY24 was at Rs. 9,391 Mn (USD 113.1 Mn) as against Rs. 8,316 Mn (USD 100.5 Mn) in the corresponding quarter last year, recording a growth of 12.9%.

In terms of secondary sales, Glenmark's India business continued to outperform the overall industry in terms of growth. As per IQVIA March 2024 data, Glenmark's India formulation business recorded growth of 11.4% in the fourth quarter, and 9.9% growth as of MAT March 2024. In comparison, the Indian Pharmaceutical Market (IPM) grew at 5.6% in the fourth quarter and 7.4% as of MAT March 2024. Glenmark continues to outperform the market in the key therapy areas of Cardiac, Dermatology and Respiratory as shown in the table below:

	IPM		GLENMARK	
SUPERGROUP	**VALUE GROWTH % (MAT MAR'24)**	**VALUE GROWTH % (JAN'24-MAR'24)**	**VALUE GROWTH % (MAT MAR'24)**	**VALUE GROWTH % (JAN'24-MAR'24)**
CARDIAC	10.7	12.3	22.4	31.0
DERMATOLOGY	6.1	8.2	9.2	11.0
RESPIRATORY	3.1	-2.3	5.5	-4.7
DIABETES	7.3	8.9	-16.4	-10.5

Glenmark's India business continues to be ranked 14th with a market share of 2.16% (IQVIA MAT March 2024). The Company continues to have 9 brands in the IPM Top 300 Brands in the country on the basis of IQVIA MAT March 2024. In terms of key therapeutic areas, Glenmark is ranked 2nd in both the Respiratory and Dermatology segments. In addition, Glenmark is now ranked 3rd in the Cardiac segment and continues to be ranked 17th in the Diabetes segment (IQVIA January-March 2024). Glenmark also has improved its market share in the key therapy areas on the back of higher growth compared to the overall industry, as noted in the table below:

	GLENMARK	
SUPERGROUP	**MARKET SHARE % MAT MAR'23**	**MARKET SHARE % MAT MAR'24**
CARDIAC	5.13	5.68
DERMATOLOGY	7.32	7.54
RESPIRATORY	5.60	5.74
DIABETES	2.33	1.82

In January 2024, Glenmark and Pfizer joined hands to launch JABRYUS® (Abrocitinib), a first of its kind oral advanced systemic treatment for moderate-to-severe atopic dermatitis (AD), in India. Developed by Pfizer,

JABRYUS® has received marketing authorization from the Central Drugs Standard Control Organization (CDSCO) in India and is approved by the U.S. Food and Drug Administration (FDA), European Medicines Agency (EMA), and other regulatory agencies. Abrocitinib is being co-marketed under the brand names JABRYUS® and CIBINQO® by Glenmark and Pfizer respectively.

INDIA – GLENMARK CONSUMER CARE (GCC)

Primary sales for GCC in Q4 FY24 was Rs. 673.2 Mn with a YoY growth of 3%. For the full year 2024, the GCC business recorded sales of Rs. 2,570 Mn with a YoY growth of 14%. The Company's flagship brand, Candid Powder™ delivered revenue growth of 3% for Q4 FY24 and 15% for full year 2024. La Shield™ portfolio delivered YoY revenue growth of 8% for the full year 2024, while Scalpe™ portfolio witnessed YoY revenue growth of 23% in full year 2024. During the year, various line extensions of the core brands performed well, particularly La Shield Expert Urban Protect and Scalpe Pro.

NORTH AMERICA

The North America business registered revenues from the sale of finished dosage formulations of Rs. 7,557 Mn (USD 91.0 Mn) for the fourth quarter of FY24 as against revenue of Rs. 8,628 Mn (USD 105.3 Mn) for the fourth quarter of FY23, and Rs. 7,629 Mn (USD 91.6 Mn) for the third quarter of FY24. This translates in to a YoY decline of 12.4% and a quarter-on-quarter (QoQ) decline of 0.9%. The overall business growth remained challenging on account of lack of new product launches and delay in scale-up of recent launches.

In FY24, Glenmark was granted final approval of three Abbreviated New Drug Applications (ANDAs): Saxagliptin Tablets, Apremilast Tablets, and Tacrolimus Ointment, 0.03%. In the fourth quarter of fiscal year 2023-24, Glenmark launched Levocetirizine Dihydrochloride Tablets USP. Glenmark also launched several products under licensing agreements, including Varenicline Tablets, Fosphenytoin Sodium Injection USP, and Ketorolac Tromethamine Injection, to name a few. The Company filed a total of 6 ANDA applications with the U.S. FDA throughout the fiscal year. The Company filed two ANDA applications with the U.S. FDA in Q4 FY24.

Glenmark has also leveraged its strong development capabilities in the Respiratory therapeutic area to build a portfolio for the US market. The Company has filed two ANDAs for generic nasal sprays and is awaiting approval for the same. In addition, the Company has filed the ANDA for gFlovent® 44mcg pMDI in May 2024. Glenmark also plans to file at least one more generic respiratory pMDI in the U.S. in FY25 and continue filing momentum beyond FY25.

Glenmark's marketing portfolio through March 31, 2024 consists of 193 generic products authorized for

distribution in the U.S. market. The Company currently has 52 applications pending in various stages of the approval process with the US FDA, of which 21 are Paragraph IV applications.

Glenmark Canada filed three ANDS applications with the Canadian Health Authorities this quarter and plan to file 2 additional ANDS next quarter. For fiscal year 2023-24, Glenmark Canada filed four ANDS applications.

All brand names and trademarks are the property of their respective owners. IQVIA National Sales Perspectives: Retail and Non-Retail, February 2024

Change in Leadership for the North America business:

Marc T. Kikuchi will be joining the Company, as President and Business Head, North America, effective 28 May, 2024. Marc joins Glenmark from Dr. Reddy's Laboratories Ltd., where he had been CEO – North America Generics since 2019. He has also worked with Zydus Pharmaceuticals and Amerisourcebergen Corporation amongst other organizations in the pharmaceutical industry. In a career spanning over 3 decades, Marc has held multiple and diverse roles of increasing responsibility. He is a graduate in Molecular and Cell Biology from University of California at Berkeley, and has a MBA from Carnegie Mellon University.

EUROPE

Glenmark Europe operations' revenue for the fourth quarter of FY24 was at Rs. 6,118 Mn (USD 73.7 Mn) as against Rs. 6,078 Mn (USD 74.6Mn) in Q4 FY23, recording a YoY growth of 0.9%.

Glenmark's European operations continued to remain strong in terms of overall business performance. While the branded markets in the region have performed well, overall growth in the fourth quarter is impacted due to softness in the tender market. Key branded markets across the CEE region such as Poland and Slovakia recorded double-digit growth in the quarter. The Respiratory portfolio launched by Glenmark in Europe continues to do well. Key brands such as RYALTRIS® and SALMEX® / ASTHMEX® continue to sustain their 15%+ market share, both, in terms of volume as well as value, across the key CEE markets. The Company continues to focus on sustaining the increasing contribution from the branded markets / portfolio in Europe. It is awaiting approval of four respiratory products which were filed in Q4 FY23. The Company is also planning to launch WINLEVI® in select markets in Europe in FY26.

ROW REGION (RCIS, LATAM, MEA & ASIA)

For the fourth quarter of FY24, revenue from the ROW region was Rs. 7,528 Mn (USD 90.7 Mn) as against Rs. 6,864 Mn (USD 83.9 Mn) for the corresponding quarter last year, recording a YoY growth of 9.7%.

As per IQVIA data, Glenmark Russia secondary sales recorded growth of 36% and 20% in Q4 FY24 and MAT

March 2024. In terms of key therapeutic areas, Glenmark recorded growth of 25% in value in the Dermatology segment versus the overall Dermatology market growth of 11% as per MAT March 2024. Amongst the Dermatology companies in Russia, Glenmark continues to rank 9th as per IQVIA MAT March 2024. In the Respiratory expectorants market, Glenmark grew in line with the overall retail market (8.1% vs. 8.6% respectively) in value as per IQVIA MAT March 2024. Amongst the companies present in the Respiratory expectorants market in Russia, Glenmark continues to maintain a strong position, ranking 2nd as per IQVIA MAT March 2024. RYALTRIS® continues to gain market share in the allergic rhinitis market.

LATAM witnessed strong growth in Q4 FY24 with the Respiratory portfolio being the key contributor in this region. Glenmark Brazil achieved high single-digit growth in the covered market as per IQVIA YTD March 2024. The Company maintained its rank in the top-10 amongst the top companies in the covered market of the chronic respiratory segment in Brazil as per IQVIA MAT March 2024. Glenmark launched the first generic Salmeterol + Fluticasone MDI in the Brazilian market in Q4 FY24 and full impact of the launch will be visible in FY25. Secondary sales growth continued to be strong in Mexico; within the covered market, Glenmark continues to rank in the top-10 as per IQVIA MAT March 2024 data. RYALTRIS® has been approved in Mexico and will be launched soon.

In the Middle East and Africa region, the Company continued to achieve secondary sales growth in Kenya, South Africa, Saudi Arabia and the UAE. RYALTRIS® continues to be the leading nasal spray for Allergic Rhinitis in South Africa, and the product was launched in key markets such as Kenya and Saudi Arabia in FY24. RYALTRIS® is also expected to be launched in other key MEA markets such as the UAE in the forthcoming quarters.

The Asia region for Glenmark recorded subdued growth in secondary sales across its key markets, mainly due to macro-economic challenges in some countries of the region. Top contributing brands in the Dermatology and the Respiratory segments have registered good growth in the fourth quarter. Glenmark received approvals for multiple new products in the region, mainly in the Dermatology, Respiratory and Oncology therapeutic areas. RYALTRIS® continues to do well across the Asia region.

CREATING GLOBAL BRANDS

RYALTRIS®

- As of March 2024, marketing applications for RYALTRIS® have been submitted in more than 80 countries across the world and the product has been commercialized in 34 markets.
- Key launches in FY24 included Canada, Saudi Arabia, Slovakia, and Kenya. Further, the product is planned to be launched in 14 other markets over the next 12 months.

- Glenmark's commercial partner in the USA, Hikma, recorded substantial increase in last quarter performance on a QoQ basis backed by strong demand and increasing coverage across major pharmacy chains and online platforms.
- Menarini, Glenmark's partner in the EU, has witnessed steady increase in market share across all its markets.
- Glenmark's partner in Mainland China, Grand Pharmaceutical (China) Co. Ltd., has received acceptance of the NDA in February 2024. The Company expects approval to be received in FY26.
- As per IQVIA December 2023 data across markets, RYALTRIS® has seen robust performance in terms of both value and unit market shares. Below are the value market shares of RYALTRIS® across key geographies (Top 10 products within "R1A1 – Nasal Corticosteroids without Anti Infectives" category as per IQVIA + RYALTRIS® as of December 2023):

MARKET	MARKET SHARE (MAT Dec'2023)	MARKET SHARE (Oct-Dec 2023)
South Africa	18.2%	19.6%
Czech	17.5%	19.7%
Australia	17.0%	17.4%
Italy	12.6%	14.3%
Poland	10.9%	11.9%
South Korea	8.7%	9.6%
Finland	7.0%	10.6%
Austria	6.1%	9.4%
Ecuador	5.4%	5.9%
Ireland	4.9%	7.5%
France	4.8%	7.2%
USA	4.3%	5.7%
Kenya	4.2%	15.6%
Spain	3.9%	5.1%
Belgium	3.7%	4.9%

Envafolimab

- In January 2024, Glenmark announced the signing of a license agreement with Jiangsu Alphamab Biopharmaceuticals Co., Ltd (Jiangsu Alphamab) and 3D Medicines (Beijing) Co., Ltd. (3DMed) for Envafolimab for India, Asia Pacific, Middle East and Africa, Russia, CIS, and Latin America.
- Envafolimab, under the brand name ENWEIDA®, has been approved in China by the National Medical Products Administration (Chinese NMPA) in November 2021 as the global-first subcutaneous injection PD-L1 inhibitor for the treatment of adult patients with previously treated

microsatellite instability-high (MSI-H) or deficient MisMatch repair (dMMR) advanced solid tumor.

- Over 30,000 patients have already greatly benefited from this innovative treatment in China where, in December 2023, it has also been officially included in the "List of Breakthrough Therapies" by the NMPA.
- Up until November 2023, Envafolimab was recommended by 12 clinical guidelines in China and the US including 3 Chinese versions of the National Comprehensive Cancer Network (NCCN) guidelines for the treatment of multiple malignancies such as tumors of the GI tract, gynecological tumors, and immune checkpoint inhibitors. Envafolimab has the potential to provide an effective treatment for such population across India and Emerging Markets.
- Envafolimab is currently also being developed in the USA by Tracon Pharma in a pivotal trial in soft tissue sarcoma (STS) subtypes including, Undifferentiated Pleomorphic Sarcoma (UPS) and the genetically related myxofibrosarcoma (MFS).
- Glenmark plans to file Envafolimab in more than 30 markets in FY25 and the first market launch is expected in FY26

WINLEVI®

- In Q2 FY24, Cosmo Pharmaceuticals N.V. ("Cosmo") and Glenmark, announced the signing of distribution and license agreements for WINLEVI® (clascoterone cream 1%) in 15 European countries as well as the UK and South Africa.
- The Company plans to launch WINLEVI® in its licensed markets starting FY26

GLENMARK LIFE SCIENCES LTD. (GLS)

In September 2023, Glenmark had announced that it has entered into a definitive agreement with Nirma Limited to divest 75% stake in its subsidiary, Glenmark Life Sciences Limited (GLS) for an aggregate consideration of Rs. 56,515 Mn, subject to closing adjustments. In March 2024, the Company completed the closing formalities of the divestment and Glenmark continues to own 7.84% in GLS after the divestment.

ICHNOS GLENMARK INNOVATION (IGI)

The Company and its global fully integrated, clinical-stage biotech subsidiary, Ichnos Sciences Inc. (Ichnos), recently announced the launch of their alliance – Ichnos Glenmark Innovation – to accelerate new drug discovery in cancer treatment. This alliance combines Glenmark's research and development proficiencies in small molecules with those of Ichnos in novel biologics to continue developing cutting edge therapy solutions that treat hematological malignancies and solid tumors. The newly formed IGI

features a robust pipeline of three innovative oncology molecules targeting multiple myeloma, acute myeloid leukemia and solid tumors currently undergoing clinical trials. Two of these molecules have received orphan drug designation from the U.S. FDA. Additionally, IGI has two autoimmune disease assets that have been out licensed to leading companies. Going forward, all of Glenmark group's investments on innovative assets will be channelized through the IGI alliance.

For further updates on IGI, including the pipeline assets, please log on to https://www.iginnovate.com/

KEY OBJECTIVES FOR FY25

- **Consolidated Revenue: INR 1,35,000 – 1,40,000 million**
- **R&D Investment: 7-7.25% of total sales**
- **EBITDA Margin: ~19%**
- **Consolidated CAPEX: INR 7,000 million**
- **Target double-digit PAT margin**

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May 2024 Update

About IGI

Ichnos Glenmark Innovation (IGI) is an alliance between Ichnos Sciences Inc., a global fully-integrated clinical-stage biotech company developing multispecifics™ in oncology, and Glenmark Pharmaceuticals Ltd. (Glenmark), with the aim to accelerate new drug discovery in cancer treatment. IGI combines Ichnos' research and development proficiencies in novel biologics with those of Glenmark's in new small molecules to continue developing cutting-edge therapy solutions that treat hematological malignancies and solid tumors. Harnessing the combined proficiency of over 150 scientists and a robust pipeline of novel molecules, this collaboration will leverage the capabilities of its three global centers of innovation spread across the USA, Switzerland and India to propel Innovation. For more information, visit www.iginnovate.com.

Headquartered in New York City, IGI has research and manufacturing operations at two sites in Switzerland. As a fully integrated biotechnology company with approximately 258 employees, IGI has strong capabilities in research, antibody engineering, small molecule, CMC, and clinical development of biotechnologies.

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

The proprietary BEAT® technology platform[1] is one of the basis for IGI's 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.

[1] Bispecific Engagement by Antibodies based on the TCR

Oncology Pipeline

IGI's multispecific antibody pipeline consists of four assets. This includes ISB 2301 which is in the discovery stages for application in solid tumors and ISB 2001, ISB 1342 and ISB 1442, each of which are orphan drug designated by the U.S. Food and Drug Administration (FDA) and currently in Phase 1 clinical studies for relapsed/refractory multiple myeloma. Small molecule research group in India has experienced research group and facility to work on challenging targets across different class and recently working on protein degradation. Updates of note in the last quarter are outlined below:

+ ISB 2001 was the subject of an oral presentation at the American Association of Cancer Research (AACR) 2024 on April 7, 2024, in San Diego, California and available online here.

MOLECULE MECHANISM/CLASS	PHASE/STATUS	LEAD INDICATION
ISB 2001 BCMA x CD38 x CD3 TREAT™ trispecific antibody[2]	Phase 1	Relapsed/Refractory Multiple Myeloma
ISB 1442 CD38 x CD47 BEAT® biparatopic bispecific antibody	Phase 1	Relapsed/Refractory Multiple Myeloma; Phase 1 study in Acute Myeloid Leukemia (AML) is planned by early 2024
ISB 1342 CD38 x CD3 BEAT® bispecific antibody[3]	Phase 1	Relapsed/Refractory Multiple Myeloma; T-Cell Acute Lymphoblastic Leukemia (T-ALL) is also under consideration
GRC 65327 Cbl-b Inhibitor	IND-enabling	Solid Tumors

IGI is looking for asset-level and platform-level collaboration partners in development and research. For more information, visit https://IGInnovate.com/contact/.

Overview of Select Oncology Drug Product Candidates

ISB 2001 TREAT™ TRISPECIFIC ANTIBODY

- ISB 2001 is a first-in-class T cell-engaging antibody that targets BCMA and CD38 on multiple myeloma cells. It is a trispecific antibody based on IGI's proprietary BEAT® platform, allowing maximal flexibility and excellent manufacturability of full-length multispecific antibodies.

[2] Trispecific Engagement by Antibodies based on the TCR.
[3] Asset available for in-licensing. Future clinical development will be advanced by a partner.

- 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.
- 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.
- At the recent AACR Annual Meeting 2024, an oral presentation showcased the results of ISB 2001 anti-myeloma activity in bone marrow aspirates from patients who were either newly diagnosed or suffer from r/r MM following multiples lines of treatment, including patients relapsing after CD38 and BCMA targeted therapies. This pre-clinical study shows the promise of ISB 2001 trispecific antibody targeting BCMA and CD38 against multiple myeloma, and CD3 on T cells.
  + ISB 2001, a BCMA and CD38 dual targeting T cell engager, demonstrates superior cytotoxicity relative to teclistamab in the samples of patient relapsing from CD38 and BCMA targeted immunotherapies.
- In April 2023, Ichnos 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. IGI 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.
- First patient was dosed in November 2023.
- In April 2024, IGI received approval from DCGI in India to expand the clinical Phase 1 study into India.
- The bulk drug substance is manufactured in La Chaux-de-Fonds, Switzerland.

ISB 1442 (CD38 X CD47 BEAT® BISPECIFIC ANTIBODY)

- This first-in-class biparatopic bispecific antibody targeting CD38 and CD47 was generated by scientists in IGI's 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 6 (450 mg SQ weekly) in both countries. The DCGI in India has recently approved the study and enrollment in India was recently initiated.
- IGI is also considering the potential development of 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 preclinical models in other hematologic malignancies were presented at the 2022 ASH Annual Meeting in December. Specifically, data showed the rationale for advancing to a clinical study in relapsed/refractory AML (link). ISB 1442 induces killing, including ADCP and ADCC, in AML cell lines in multiple in vitro assays. ISB 1442 also showed 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 in IGI's manufacturing plan in La Chaux-de-Fonds, Switzerland.
- Additional information on the ongoing Phase 1 was presented at the 2023 ASH Annual Meeting. Overall, treatment of low grade (1 or 2) CRS and mostly resolved within one day. No neurotoxicity events have been observed to date. No signal infections or anemia. https://www.hematology.org/meetings/annual-meeting/abstracts
  - Proof of Mechanism in patients was declared based on increased macrophage-related markers among the other biomarkers changes observed.
  - Dose escalation is ongoing.

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
  - The study has been suspended and is available for partnerships due to pipeline strategic reprioritization. The out-licensing of this asset will allow a potential partner to continue the escalation/expansion now that clinical proof-of-mechanism and proof-of-concept have been established with acceptable immunogenicity on par with other bispecifics.
  - The Database has been locked and all sites closed by Q2, 2024. The Clinical Study Report is targeted for H2, 2024.
  - The first partial response in this study was observed in Cohort 109 intravenous (dose level 8 µg/kg) and additional two partial responses were observed in Cohort 110 intravenous (dose level 16 µg/kg). The responses are supported by translational data, where higher T-cell activation has been observed with increasing doses.
- The primary objectives of the Phase 1 study are to:
  - Determine maximum tolerated dose and/or recommended Phase 2 dose of ISB 1342 (Part 1 dose escalation).
  - Assess the 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 2023 American Society of Hematology (ASH) Annual Meeting in December (link) with data cut-off October 27, 2023:
  - 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
  - Further dose-escalation (to 32 and 64 µg/kg) is warranted based on the manageable safety profile, anti-myeloma activity observed, and supported by PK profile as well as T-cell activation biomarkers.
- ISB 1342 was granted Orphan Drug Designation for multiple myeloma by the U.S. Food and Drug Administration.
- The bulk drug substance is manufactured in IGI's manufacturing plant in La Chaux-de-Fonds, Switzerland.

CASITAS B-LINEAGE LYMPHOMA B (CBL/B) PROGRAM

- Casitas B-lineage lymphoma b (Cbl/b) is an E3 ubiquitin ligase that has been identified as a key inhibitor of T cell activation in the absence of CD28 co-stimulation and considered as intracellular check point. Through a complex interaction of signal transducers, Cbl-b inhibits T cell transcriptional activity and promotes immune tolerance across innate and adaptive immunity. As an intracellular master regulator, Cbl/b inhibition may represent a more specific and efficient route toward broad immune activation regardless of upstream checkpoint signalling (i.e., PD-1, CTLA-4). Substantial preclinical evidence supports Cbl/b inhibition as a potent driver of anti-tumor immunotherapy.

- GRC 65327 is the clinical candidate. It has been identified as a novel nanomolar potent, selective, and orally bioavailable candidate with intuitive medicinal chemistry and computational chemistry approaches.

- IND-enabling studies are ongoing. The clinical formulation will be ready by mid-October 2024.

- The submission to the Drugs Controller General of India (DCGI) is planned at the end of CY24 and the FIH trial is expected to start in early 2025 and enroll patients with relapsed/refractory solid tumor indications.

Autoimmune Diseases

IGI has two monoclonal antibody drug product candidates addressing autoimmune diseases in the pipeline. 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) and its follow-on molecule ISB 830-X8, was licensed to Astria Therapeutics in October 2023. Telazorlimab is an OX40 antagonist that successfully completed a Phase 2b study in moderate to severe atopic dermatitis in 2021. 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	Licensed to Astria Therapeutics in October 2023. Successfully completed a Phase 2b study in Atopic Dermatitis.
	Other autoimmune diseases, including Rheumatoid Arthritis	U.S. IND for Rheumatoid Arthritis and other autoimmune indications is active.	
	Other autoimmune diseases, including Rheumatoid Arthritis	U.S. IND for Rheumatoid Arthritis and other autoimmune indications is active.	

ISB 880 / ALM27134 (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

- For more information on this asset, please visit almirall.com

ISB 830 (TELAZORLIMAB, OX40 ANTAGONIST)

- Ichnos entered an exclusive global licensing agreement for ISB 830 in autoimmune diseases with Astria Therapeutics in October 2023.

- Previously, Ichnos had received FDA clearance to study Telazorlimab in seropositive autoimmune diseases (Rheumatoid Arthritis, Systemic Lupus Erythematosus, Sjogren's Syndrome, Multiple Sclerosis, Type I Diabetes Mellitus, Myasthenia Gravis).

- For more information, visit https://IGInnovate.com/contact/.