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	Bioshares Portfolio
Year 1 (May '01 - May '02)	21.2%
Year 2 (May '02 - May '03)	-9.4%
Year 3 (May '03 - May '04)	70.6%
Year 4 (May '04 - May '05)	-16.3%
Year 5 (May '05 - May '06)	77.8%
Year 6 (May '06 - May '07)	17.4%
Year 7 (May '07 - May '08)	-35.8%
Year 8 (May '08 - May '09)	-7.4%
Year 9 (May '09 - May '10)	50.2%
Year 10 (May '10 - May'11)	45.4%
Year 11 (May '11 - May '12)	-18.0%
Year 12 (May '12 - May '13)	3.1%
Year 13 (May '13 - May '14)	26.6%
Year 14 (May '14 - May '15)	23.0%
Year 15 (May '15 - May '16)	33.0%
Year 16 (May '16 - May '17)	16.8%
Year 17 (May '17 - May '18)	-7.1%
Year 18 (May '18 - May '19)	-2.3%
Year 19 (May '19 - May '20)	39.5%
Year 20 (May '20 - May '21)	86.8%
Year 21 (May '21 - May '22)	-15.6%
Year 22 (May '22 - Dec '22)	-2.2%
Year 23 (CY2023)	-15.4%
Year 24 (CY2024)	-1.2%
Cumulative Gain	1304%
Av. Annual gain (23 yrs)	16.6%

Companies covered: **ACR, ARX, IMC, LBT, LDX, Myopharm, MX1, RNO, RSH, SOM, TLX, Obesity drug feature**

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BIOSHARES

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Extract from Bioshares –

Private Company Feature

Myopharm - Commercialising a Novel Combination Therapy for Type 2 Diabetes

Myopharm is an unlisted biotech that was previously focused on the development of therapeutics for Duchenne's Muscular Dystrophy (DMD).

In 2021, the company pivoted its focus to treatments for diabetes. Myopharm's pipeline includes seven pre-clinical candidates, although TriGlytza (RK-01) for the treatment of type-2 diabetes (T2D) is the company's primary focus.

The company is developing TriGlytza as an adjunctive therapy to current 'blockbuster' anti-diabetic drugs (ADDs) such as metformin (now a generic) and Novo Nordisk's Ozempic. Metformin alone generates over 91.5 million prescriptions annually in the U.S.[(1)]

TriGlytza is a combination of two existing drugs which are now generics; celecoxib, a selective COX-2 inhibitor (originally sold as Celebrex), and valsartan, an angiotensin receptor (AT1R) blocker (originally sold as Diovan). Celecoxib is a strong anti-inflammatory drug. And valsartan has several applications, but is primarily purposed for the reduction of high blood pressure, which can incidentally help in treating diabetic renal (kidney) complications.

COX-2 and AT1R are found to be upregulated in the pancreas of patients with T2D compared to non-diabetics.[(2),(3)] They have both been found to promote beta cell deterioration.[(2),(3)] Beta cells are found in the islets in the pancreas and are necessary for insulin production. (See the cut-out box for TriGlytza's detailed mechanism of action.)

Value Proposition for TriGlytza

TriGlytza, Myopharm claims, is uniquely positioned to serve the diabetes market as an add-on therapy. Currently marketed drugs (including GLP-1s, SGLT2 inhibitors, and DPP4 inhibitors) fail in approximately 50% of patients within an average period of 16 months in the U.S.[(4)]

However, by inhibiting pancreatic beta cell deterioration, TriGlytza has the potential to improve existing therapies, with the main patient targets being those who are treatment-naive (to preserve existing beta cells) or treatment-ineffective (by restoring beta cell function).

Currently available diabetes drugs lack satisfactory long-term effectiveness, which is likely due to their failure in addressing the underlying pathophysiology of T2D, according to Myopharm. As an example, metformin's efficacy is dependent on the body's ability to produce insulin.

The lead scientist who developed the product concept of TriGlytza, Dr. Ravi Kumar,

Continued over

stated that no currently marketed drugs directly and adequately address the damaging pro-inflammatory signals that promote beta-cell deterioration in T2D. TriGlytza directly addresses beta-cell deterioration by reducing prostaglandin-E2 (PGE2) levels. PGE2 is a pro-inflammatory molecule causing beta-cell deterioration.[2] *(See mechanism of action description).*

COX-2 Inhibitors and the Safety of TriGlytza

The safety of COX-2 inhibitors has been questioned in the past. This resulted in another COX-2 inhibitor, Vioxx, being taken off the market in 2004 due to an increased risk of heart attacks.

Presumably this prompted Pfizer, which sells the branded celecoxib drug Celebrex, to conduct a 20-month treatment study in 24,000 patients who were followed for an additional 34 months.[7] That study, called the PRECISION trial, recruited patients with an increased cardiovascular risk. Patients were given either Celebrex twice daily (100-200mg oral tablets) or ibuprofen (600-800 mg three times a day) or naproxen (another COX-2 inhibitor). The trial started in 2006 and concluded in 2016.

The results showed there were fewer renal events with Celebrex with a more favourable cardiovascular safety profile compared to ibuprofen and naproxen. This resulted in the FDA softening the label for celecoxib (Celebrex) in 2018 at the lower dose of 200mg per day. There was insufficient data on patients taking the higher dose of Celebrex in that study.

Of interest to note is that celecoxib (Celebrex) selectively inhibits COX-2, where naproxen, ibuprofen and Vioxx inhibit both COX-1 and COX-2 enzymes non-selectively, often giving rise to gastrointestinal side effects (due to the inhibition of the COX-1 enzyme).

Valsartan has demonstrated good safety profile in a variety of patients.[8]

Myopharm has acquired the rights to the TriGlytza IND from ARKAY Therapeutics. The IND submission to the FDA for TriGlytza elicited no questions about the safety concerns of TriGlytza, which the company cites as "a welcome and encouraging development."

Efficacy

Data from studies conducted by others has shown celecoxib has restored insulin sensitivity in a study with 12 obese patients.[9] In a preclinical study in mice (by others), valsartan was shown to restore beta cell dysfunction as well as enhance blood flow (which could improve complications in T2D from poor blood circulation).[10] Myopharm believes that the combination of celecoxib and valsartan could produce a synergistic effect providing a greater than additive effect when combining the treatments.

IP and Background of Technology TriGlytza

The inventor of this technology being commercialised by Myopharm is Dr Ravi Kumar. The technology was originally being developed by Dr Kumar at ARKAY Therapeutics. Dr. Kumar has over 30 years of academic and pharmaceutical industry experience which includes work at The Cleveland Clinic Foundation and at Pfizer. Dr Kumar currently works for Johnson & Johnson.

The full IP rights of TriGlytza as well as the IND cleared by the FDA (ClinicalTrials.gov ID: NCT 036866757) were purchased by Myopharm in December 2023 from ARKAY Therapeutics LLC, following a three-year collaboration. The purchase price remains undisclosed.

ARKAY Therapeutics sold TriGlyzta (RK-01) to Myopharm after a paucity of funding during the COVID-19 pandemic. The purchase included a US patent (US 9,839,644 B2) covering formulation and use with 68 metabolic claims associated with TriGlytza (including T2D, PCOS, and NASH as well as an IND). To maximise patent security, Myopharm is applying for a Chinese IND and a paediatric claim that may be eligible for an orphan drug designation for major markets.

Myopharm's existing patent expires in September, 2034. The company intends to explore patent-extension options, which includes new commercial product formulations. Dr Kumar remains an advisor to Myopharm.

Structure of the upcoming Phase I clinical trial

Phase I clinical trials for TriGlytza will be conducted after completion of Myopharm's next capital raise. The study is expected to provide information on the optimal dose with some early efficacy data. The trial will include four separate arms including one control group (see table on previous page). All participants will continue with the dose of metformin recommended by their healthcare practitioner. The treatment period of the study will be 26 weeks with an interim analysis after 12 weeks of treatment.

During the clinical trial, patients will take once-daily TriGlytza (morning) and once-daily metformin. Trial recruitment is not anticipated by Myopharm to be particularly challenging. The estimated cost of the trial is $1.7 million. If the trial is conducted in Australia the company will be eligible for a 43.5% tax rebate on expenses.

Myopharm intends to follow a 505(b)(2) pathway for regulatory approval with the FDA. This process references the previous safety data from the individual components of the therapy prepared by other drug developers, which potentially offers a faster path to market for the Myopharm therapy.

Forthcoming Phase I clinical trial design

Arm 1 (N=25)	Metformin only (control)
Arm 2 (N=25)	Metformin + TriGlytza (Low/subtherapeutic dose)
Arm 3 (N=25)	Metformin + TriGlytza (Medium dose)
Arm 4 (N=25)	Metformin + TriGlytza (High dose)

Continued over

Myopharm's Capital Raising Plans

Myopharm has raised $2.9 million from sophisticated investors over the past three years. The last funding round raised $0.7 million at $0.16 per share in 2023.

Myopharm is intending to conduct a larger raise of $2 million in the second half of CY2024 in preparation for the Phase I TriGlytza clinical trial. Additionally, the company is not solely reliant on investors due to OMNI-D® royalties. (See FSMP Business below).

The company is not considering an IPO in the near-term.

FSMP Business

Myopharm partly funds its R&D activities from its Food for Special Medical Products (FSMPs) such as OMNI-D. OMNI-D is an over-the-counter product commercialised by Myopharm and developed over a decade by Adelaide University and the Baker Heart and Diabetes Institute. OMNI-D improves glycaemic control by reducing post-prandial glucose spikes by 36.5%.[11]

Ongoing discussions are underway in Japan, South Africa, and the U.S. for potential multinational licensing of OMNI-D. Myopharm's other FSMP products include WHOLESLIM and OMNI-S. Revenue from these products have not been disclosed.

Epidemiology & market opportunities

Diabetes is the "fastest growing chronic condition globally.[12] According to projections by the International Diabetes Federation (IDF), one in eight adults (783 million) will be living with T2D by 2045, marking a rise of 46% from 2023 levels. This rate is more than double the expected population growth (20%) over the same period.[13]

The global T2D market alone was worth USD$32 billion in 2022.[14] It is expected to surpass USD$70.1 billion by 2032 (registered CAGR = 8.20%).

Continued over

TriGlytza's Proposed Mechanism of Action

TriGlytza is a beta-cell centric dual-combination (add-on) drug that proposes to mitigate progressive beta-cell deterioration by reducing levels of pro-inflammatory mediators – primarily, PGE2. For TriGlytza to be effective, it will be necessary for patients to have a critical mass of pancreatic beta-cells.

TriGlytza consists of celecoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, and valsartan, a selective angiotensin receptor 1 (AT1R) blocker. These inhibitors each block targets in the linear axis of the Renin-Angiotensin pathway to directly minimise the production of PGE2 in pancreatic islets.[1] PGE2 promotes apoptosis in pancreatic beta-cells.[1]

COX-2 and AT1R are upregulated in the pancreatic islets of T2D patients, compared against human islets from non-diabetic patients.[2], [3] Both contribute to reduced beta-cell function and promote beta-cell deterioration.[2], [3]

COX-2 upregulation in T2D drives the IL-1beta/COX-2/PGE2 pathway loop.(2) Here, increased COX-2 activity increases levels of pro-inflammatory cytokines (IL-1beta and PGE2) which drive beta-cell apoptosis.[2] It has been demonstrated that administering Celecoxib restores the expression of critical beta-cell genes (such as PDX1, NKX6.1, and MAFA).[2]

AT1R upregulation in T2D drives oxidative stress, apoptosis, and fibrosis which ultimately diminishes pancreatic islet lifespan.[3] AT1R overexpression also inhibits (pro) insulin biosynthesis and glucose-sensitive insulin release by impairing islet blood flow.[3] It has been demonstrated that valsartan improved insulin secretion in T2D patients.[4]

The design of TriGlytza includes an immediate-release (IR) of celecoxib and a delayed-release (DR) of valsartan. According to Myopharm, this is because in simultaneous release formulations, Celecoxib has been demonstrated to reduce the efficacy of valsartan. And so, due to the staggered release of each component drug in TriGlytza, the effects of celecoxib and valsartan become additive and synergistic more effectively reducing PGE2 levels compared to if either were acting alone.

The therapeutic profiles of celecoxib and valsartan present good arguments for their wider distribution for the treatment of T2D. This consideration influenced the pharmacokinetic profile design of TriGlytza to be non-tissue restrictive. The broader reach can potentially benefit a significant portion of T2D patients with comorbidities such as hypertension (85%) and arthritis (47%). Valsartan is an antihypertensive with well-established clinical use and celecoxib is used to treat arthritis.[1]

While Myopharm has completed the tablet formulation for TriGlytza, the dual-combination pill in a capsule form is currently in development. Myopharm is also currently conducting bioequivalent studies.

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Summary

One current challenge impeding the expansion of the overcrowded, generic (as well as branded) diabetic drugs market is the paucity of sustained, long-term therapeutic efficacy in many patients.

Myopharm's value proposition for TriGlytza addresses this pertinent gap. The company believes that TriGlytza can become a lucrative add-on treatment option. The scientific rationale appears to be well substantiated.

An area that the company could strengthen is patent protection around the technology.

The key challenge and milestone ahead for the company is to obtain sufficient funding to conduct its Phase I/II clinical study.

Investors interested in learning more about Myopharm should conduct Karinza Phoenix, Executive Chair and founding CEO. (kphoenix@myopharm.com)

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Bioshares

How Bioshares Rates Stocks

For the purpose of valuation, Bioshares divides biotech stocks into two categories. The first group are stocks with existing positive cash flows or close to producing positive cash flows. The second group are stocks without near term positive cash flows, history of losses, or at early stages of commercialisation. In this second group, which are essentially speculative propositions, Bioshares grades them according to relative risk within that group, to better reflect the very large spread of risk within those stocks. For both groups, the rating "Take Some Profits" means that investors may re-weight their holding by selling between 25%-75% of a stock.

Group A

Stocks with existing positive cash flows or close to producing positive cash flows.

Buy	CMP is 20% < Fair Value
Accumulate	CMP is 10% < Fair Value
Hold	Value = CMP
Lighten	CMP is 10% > Fair Value
Sell	CMP is 20% > Fair Value

(CMP–Current Market Price)

Group B

Stocks without near term positive cash flows, history of losses, or at early stages of commercialisation.

Speculative Buy – Class A
These stocks will have more than one technology, product or investment in development, with perhaps those same technologies offering multiple opportunities. These features, coupled to the presence of alliances, partnerships and scientific advisory boards, indicate the stock is relative less risky than other biotech stocks.

Speculative Buy – Class B
These stocks may have more than one product or opportunity, and may even be close to market. However, they are likely to be lacking in several key areas. For example, their cash position is weak, or management or board may need strengthening.

Speculative Buy – Class C
These stocks generally have one product in development and lack many external validation features.

Speculative Hold – Class A or B or C

Sell

Corporate Subscribers: Cogstate, Syntara Dimerix, Patrys, Imugene, Chimeric Therapeutics, Neuren Pharmaceuticals, Aroa Biosurgery, Anteris Technologies, EBR Systems, Immuron, Respiri, Clinuvel Pharmaceuticals