Ian Haydock (00:09):

Hello and welcome to the podcast version of Scrip's Five Must-know Things. This time for the business week ended June 30th, 2023. This is Ian Haydock.

This time —Lilly wows ADA with obesity results; Novo's oral semaglutide data, first DMD gene therapy approved; the outlook for biopharma fundraising; and Korean pharma considers strategy in a changing world.

Eli Lilly is a few years behind Novo Nordisk in bringing a GLP-1 agonist to market for obesity, but it presented data at the American Diabetes Association or annual meeting that could give the company a best-in-class portfolio of medicines, including its GLP-1/GIP/glucagon (GGG) receptor tri-agonist retatrutide, which generated weight loss of up to 24.2% in overweight and obese patients without diabetes at 48 weeks. In a Phase II clinical trial presented on June 26.

[Scrips'] Mandy Jackson writes that Novo Nordisk already market the injectable GLP-1 agonist Wegovy for obesity in the US and plans to submit the high-dose oral version of semaglutide for US and EU approvals this year based on the Phase III OASIS 1 trial presented on June 25 at ADA in San Diego.

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Lilly's injectable GLP-1 GIP agonist Mounjaro™, which the US FDA approved for type 2 diabetes in 2022 could win US approval for obesity by the end of 2023, providing the company's first entry to the US obesity market and offering a formidable competitor for Wegovy.

Lilly's slate of obesity data at ADA included Phase III results for Mounjaro in overweight and obese patients with type 2 diabetes, as well as Phase II results in non-diabetic individuals who are overweight and obese for tirzepatide as well as for orforglipron, an oral non-peptide GLP-1 agonist. The latitude drugs have moved into Phase III development — orforglipron for both type 2 diabetes and obesity, and tirzepatide or chronic weight management.

"Right now our belief is we have the broadest portfolio of type 2 diabetes and obesity treatments in various phases of development across the industry," Jeff Emek, who's senior vice president of product development at Lilly Diabetes, said in an interview at ADA.

Across GLP-1 agonists obesity presentations at ADA, including for Lilly's and other companies' drugs, experts noted that weight loss tends to be observed at higher levels in obese and overweight patients who do not have diabetes than in trials where patients' comorbidities include diabetes. For Mounjaro, Lilly reported weight loss of 21.4% for the 10-milligram, once-weekly dose of the drug and 22.5% for the 15-milligram dose at 72 weeks in the Phase III SURMOUNT-1 trial at ADA in 2022.

Staying with ADA, Mandy also writes that the race to bring an oral obesity agent to market is

heating up. Novo Nordisk presented detailed results for the oral version of its GLP-1 agonist semaglutide on June 25 at the meeting from the Phase IIIa OASIS 1 clinical trial with 15.1% mean weight loss observed in overweight and obese adults versus 2.4% for placebo, confirming topline results released in May.

The readout took place two days after the presentation of Phase II data at ADA for Lilly's oral GLP-1 drug orforglipron, which could be a formidable competitor. Overweight and obese adults treated with the highest dose of orforglipron achieved weight loss of 14.7% at 36 weeks in Lilly's phase two study, and the weight reductions did not plateau before the end of the 36-week trial. Both Novo's OASIS 1 trial and Lilly's phase two trial recruited overweight and obese adults with at least one comorbidity excluding type two diabetes.

While Novo plans to submit its once-daily all or semaglutide 50-milligram dose for US and EU approvals as a treatment for obesity in 2023, the company has not committed to specific filing or launch timelines, which are dependent on Novo's capacity to supply its US-approved injectable version of semaglutide, Wegovy.

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While Wegovy has had an impressive obesity launch that is injectable GLP-1/GIP agonist, Mounjaro, cleared by the FDA for type two diabetes in 2022, could be approved in the US by the end of 2023, based on the Phase III SURMOUNT-1 and SURMOUNT-2 trials. Detailed results from SURMOUNT-2, which enrolled overweight and obese patients with type 2 diabetes, were presented at ADA, showing mean weight loss of 13.4% for the 10-milligram weekly dose and 15.7% for the 15-milligram weekly dose at 72 weeks.

Besides orforglipron, a third oral GLP-1 competitor also is close behind oral semaglutide and Lilly's drug, since Pfizer has two GLP-1 drugs in Phase II, with data expected later in 2023 and early in 2024, which will inform the company's decision about whether to move its once-daily or twice-daily molecule into Phase III.

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Sarepta Therapeutics is confident its newly approved gene therapy for Duchenne muscular dystrophy or DMD, Elevidys, will be a commercial despite initial age restrictions and carrying a price tag of $3.2 million. The company has worked at being transparent around pricing and believes "the work that we've done to support the pricing of this therapy is potentially a blueprint for others," CEO Doug Ingram said during a June 22nd analyst call about the approval.

Jessica Merrill and Mary Jo Laffler, write that the US FDA, granted an accelerated approval to Sarepta's gene therapy, although the approval is for a narrow indication in children 4 to 5 years old and is based on a surrogate endpoint expression of dystrophin protein, rather than a clinical endpoint.

Wholesale acquisition costs for the gene therapy is $3.2 million, although "nearly all infusions

will be subject to a statutory discount for Medicaid or 340B discounts, so with distribution and other discounts, you should be modeling a gross to net adjustment in the mid-20% range., Ingram told the call.

The price tag is well below what the company could have tried to justify. On May 26, it published an article in the *Journal of Market Access & Health Policy* using an established pharmacoeconomic model, which concluded that as a one-time treatment Elevidys is cost-effective at a price of $5 million to $13 million.

While the company said it's “ready to serve the market today,” there are some steps that have to happen before a patient is dosed, including securing reimbursement agreements with payers. Ingram cautioned that the ramp up will be slow, similar to that seen for Sarepta's earlier DMD products, Exondys, Amondys and Vyondys, due to the size of the population and the additional gene therapy steps,” such as screening for neutralizing antibodies, site procurement, and post-therapy monitoring.

Sarepta is the first company to gain approval for a DMD gene therapy, beating others to the market, including Pfizer, which has a Phase III candidate. While questions remain about Elevidys’s long-term safety and efficacy with a Phase III study still ongoing, the approval nevertheless marks an important milestone in the effort to develop a cure for DMD.

Biopharmaceutical investors and executives alike conceded during the recent international convention that the booming financial environment, which peaked in 2020 and 2021 with record levels of venture capital investment and initial public offerings, created too many new drug development startups and public companies.

Many therapeutics firms shut down as investment in the sector slowed in 2022 and early 2023 — a trend that is likely to continue — but to others have adjusted to the new market realities.

Mandy Jackson spoke with several investors and executives at BIO about their expectations for when this downturn in the financial market will turn around, but none had a clear view of when the industry could expect a significant change. Speakers on June 5th panel titled “Biopharma Dealmaking in Uncertain Times” also offered advice for keeping companies afloat until the market cycle reverses course — whenever that might happen.

Venture capital firms are investing more conservatively to preserve their existing funds for only the highest-quality startups and to back companies they funded previously. Since the IPO market largely shut down in 2022, VC investors have had to finance their portfolio companies through series B, C or later rounds to keep research and development programs going. And with fewer companies exiting their portfolios via IPOs and too few leaving via acquisitions, many VC firms are enabled to raise new funds.

Chris Garabedian, who's chairman and CEO of the biotech accelerator and investment firm Xontogeny, explained to Scrip that this has set up a musical-chairs scenario in the VC arena. VC

investors go out looking for other firms to join syndicates to back funding rounds for their portfolio companies, but their peers turn down those opportunities and at the same time ask for participation in financings for their own portfolio companies.

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Garabedian further noted that VC firms typically have a five- to 10-year investment period for their funds, but firms were investing their money more rapidly during the exuberant investment cycle before 2022 and then quickly going out to raise new funds. “Now, every VC I know is going to be taking full advantage of that investment,” he said. “That means the bar is going to get raised higher because you're going to say ‘no’ to things you would've said ‘yes’ to a couple of years ago.”

On the public company side, EY senior advisor Barbara Ryan noted during the same dealmaking panel that broader macroeconomic concerns — such as rising inflation and increased interest rates, plus the uncertainty of whether the US and other global economies are entering a recession — have caused investors to shift their money from high-risk sectors such as biopharma to lower-risk investments. That will change, but, in the meantime, the macroeconomic climate will be a major headwind for biopharma firms, Ryan said.

Amit Mehta, who's vice president and head of business development for Genentech Research and Early Development, noted that biotech firms, when they're seeking financing, whether it's through the public markets or through the private markets, the focus is on ensuring that they have a truly differentiated platform or asset.

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Finally, amid a weak global economy and big pharma cutbacks and less aggressive dealmaking, Korean biopharma firms looking to enter global markets should also adopt different strategies, according to one prominent executive in the country, Jung Won Shin writes.

Korean Drug Development fund CEO H. Samuel Muk shared his views in a recent webinar organized by EBN, noting: “They can't survive with the same strategies in a time of economic slump; ‘select and focus’ becomes a truth in the end.”

He suggested several business models according to the types of biopharma players in Korea, the first being a contract manufacturing organization model. As this may require investments of billions of dollars in production facilities, it's more suited for large firms such as conglomerates. The second model is based on using new drugs to enter major markets, something Muk viewed as appropriate for Korea's top five mainstream pharma firms.

Thirdly, next year, companies with annual sales of around 500 billion Korean, such as Dong-A ST, an affiliate of Dong-A Socio Holdings and Ildong Pharmaceutical Co., Ltd., cannot invest substantial amounts in R&D because of their limited size. As a result, their strategy will need to involve the creation of new drug development subsidiaries that could attract funding from

venture capital sources.

The fourth viable strategy for Korean firms would be to pursue continuous out-licensing deals, something that could apply largely to many biotechs listed on the Kosdaq market, which are unable to complete late clinical development and commercialization by themselves. This approach is predicated on a steady flow of pipeline assets to be partnered at the mid-development stage.

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Finally, the “pharmerging” model involves entry into large-population markets such as Southeast Asia, South Asia, the Middle East, and central South America, something that Korean firms like Korea United Pharm and Boryung could do with incrementally modified products via joint ventures and co-research deals.

Furthermore, an IPO should not be the only strategy for a bio venture, which needs to think about a sustainable business model after this to feed the R&D pipeline, generate out-licensing deals and operating profit, and find partners for global markets. In addition, firms need to get bigger through mergers with companies with similar business models to reduce costs, he suggested.

That's all for this time. Many thanks for listening. These stories form just a fraction of Scrip’s coverage last week. Log in to access all of our much more extensive content or take a free trial to see what you're missing. Bye for now!

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