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Zacks Small-Cap Research

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Organovo Holdings (ONVO-NASDAQ)

ONVO: Initiating Coverage: Technology Accelerates Drug Development

ONVO is a biotech company with dual revenue paths that compliment one another—3D technology and drug development. We value ONVO at $12.15/share using the discounted cash flow method.

Current Price (10/09/23)	$1.21
Valuation	**$12.15**

OUTLOOK

Organovo is a biotech company that has 3D technology enabling the company to produce various human tissues, allowing the company to target diseases and accelerate the drug development process.

The company is well along the drug development path, and we believe, due to studies done using 3D technology, the drug has higher potential for approval and eventual commercialization.

SUMMARY DATA

52-Week High	**$3.20**
52-Week Low	**$1.06**
One-Year Return (%)	**-37.84**
Beta	**0.84**
Average Daily Volume (sh)	**53,145**
Shares Outstanding (mil)	**9**
Market Capitalization ($mil)	**$11**
Short Interest Ratio (days)	**N/A**
Institutional Ownership (%)	**9**
Insider Ownership (%)	**4**
Annual Cash Dividend	**$0.00**
Dividend Yield (%)	**0.00**
5-Yr. Historical Growth Rates	
Sales (%)	**N/A**
Earnings Per Share (%)	**N/A**
Dividend (%)	**N/A**
P/E using TTM EPS	**N/A**
P/E using 2024 Estimate	**N/A**
P/E using 2025 Estimate	**N/A**
Zacks Rank	**N/A**

Risk Level	**Above Avg.**
Type of Stock	**Small-Value**
Industry	**Biotech**

ZACKS ESTIMATES

Revenue
(in thousands of $)

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2022	N/A	N/A	N/A	N/A	370 A
2023	75 A	75 E	75 E	75 E	300 E
2024	100 E	100 E	120 E	124 E	444 E
2025	130 E	130 E	130 E	143 E	533 E

Earnings

	Q1 (Jun)	Q2 (Sep)	Q3 (Dec)	Q4 (Mar)	Year (Mar)
2022	N/A	N/A	N/A	N/A	-$1.98 A
2023	-$0.46 A	-$0.43 E	-$0.44 E	-$0.44 E	-$1.77 E
2024	-$0.46 E	-$0.46 E	-$0.50 E	-$0.50 E	-$1.92 E
2025	-$0.45 E	-$0.45 E	-$0.46 E	-$0.49 E	-$1.85 E

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INITATION REPORT

We are pleased to be initiating coverage of Organovo Holdings (ONVO) with a price target of $12.15.

Organovo Holdings is a biotechnology company that is both a developer of 3D tissue technology that has the potential to change the way treatments are discovered and tested, as well as being a creator of new therapies using that technology, the focus of which is currently around the intestinal area and inflammatory bowel disease—something which impacts over 3 million Americans according to the CDC.

It is this dual path and how the two paths can work together that excites us about Organovo. Regarding the 3D technology, Organovo's advances in the area include cell type-specific compartments, prevalent intercellular tight junctions, and the formation of microvascular structures. Management believes these attributes can enable critical complex, multicellular disease models that can be used to develop clinically effective drugs across multiple therapeutic areas. The company's technology, known as NovoGen Bioprinters, are automated devices that enable the fabrication of 3D living tissues comprised of mammalian cells. The Company believes that the use of its bioprinting platform as well as complementary 3D technologies will allow it to develop an understanding of disease biology that leads to validated novel drug targets and therapeutics to those targets to treat disease. To this point, the company's technology has been used to create a wide variety of tissues such as: healthy liver, NASH (nonalcoholic steatohepatitis) liver, kidney, intestine, skin, vascular, bone, skeletal muscle, eye, breast and pancreatic tumor.

There are two avenues that we believe the company can benefit from this technology. First, Organovo can use the technology internally to develop drugs that able to be tailored more specifically to the targeted condition because the company can manipulate the 3D created tissues to reflect the disease as it would appear in actual human tissue. This also allows the company to move through the initial stages of research and testing in a more rapid and precise manner, which makes the process more efficient and cost effective and the treatments potentially more effective.

Additionally, many clinical stage companies have no revenue inflows to help offset the costs of developing much needed treatments. However, as already demonstrated, Organovo has the ability to license the company's 3D technology to other companies to aid in their research process, leading to a revenue stream coming into Organovo as it continues to push to bring treatments to the market. According to company management, any deal achieved with a pharma company, Organovo intends to avoid "fee for services" revenue, which it believes provides limited benefit. Instead, the company will target deals with large, up-front payments, followed by milestone payments that the company believe could be in the hundreds of millions of dollars. These deals will involve the company working with the pharma partner to push novel drugs to the market. The partner company would own the rights to the drug, but Organovo would expect to earn milestone payments as a drug advances and royalties upon a drug's commencement of commercial sales. These deals can be hard to predict the timing or probability of, but when achieved they have the potential to provide further validation of the company's science and approach, as well as being a potential catalyst for investors.

The other path is the drug development path, which is obviously complemented and fueled by the 3D technology side of the business. Organovo has the potential to develop drugs in a more cost-effective manner and at a quicker rate by using 3D-created tissue as opposed to animal subjects. This ability also has the potential to provide more effective treatments due to the testing being done

on human tissue as opposed to animal tissue, which also has the advantage of saving the animal as well.

As mentioned, the company is currently focusing on treatments surrounding IBD and the initial test results look promising and a Phase 2 trial for its signature treatment is approved to proceed by the FDA and will get started soon.

We believe Organovo is at a good spot for potential investors, with a proven technology that is bringing in revenue and is about to begin human testing on a treatment for a condition that millions of people are dealing with. Given these circumstances, we believe that investors should take a look at the following analysis to learn the details of the exciting story of Organovo and consider investing in a cutting-edge company.

THE 3-D TECHNOLOGY

We believe the starting point for what makes Organovo different from other clinical stage drug companies and worth a look for investors is the company's 3-D technology. More specifically, 3D bioprinting is an advanced technology that combines 3D printing techniques with biology to create three-dimensional structures composed of living cells, biomaterials, and other biological components. This revolutionary field has the potential to transform various aspects of healthcare, including tissue engineering, regenerative medicine, drug testing, and personalized medicine.

3D tissues exhibit tissue-like density with highly organized cellular features, such as intercellular tight junctions and microvascular networks. The ability to create architectural compartments, with different cell types placed in discrete locations relative to each other, results in a microenvironment with cell-cell interactions similar to that of native tissues. This in turn results in proper expression and localization of key cellular functions – such as key metabolic enzymes and key transporters – over several weeks in culture. The responses of 3D bioprinted tissues to acute or chronic exposure of drugs and known toxins resemble what is observed in vivo and in the clinic. Furthermore, under the right conditions, using diseased patient cells in bioprinted tissues can recapitulate the disease phenotype while healthy cells do not under the same conditions. This allows screening for targets and drugs to those targets that block disease progression in cells from an actual human patient with disease. The company believes these drugs will be fundamentally more efficacious than drugs discovered using traditional methodologies and have a higher chance of success in Phase 2 and Phase 3 studies. A drug showing promise in Organovo's platform, as a result, has the potential to be a better investment for successful development than a drug developed in traditional animal models alone.

1. **Drug Testing and Development:** 3D bioprinting can be used to create functional tissue models for drug testing. These models can replicate the complexity of human tissues and organs, providing a more accurate platform for studying the effects of drugs and toxins. This can help streamline drug development processes and reduce the need for animal testing.

2. **Disease Modeling:** Bioprinted tissues and organs can be used to create disease models, allowing researchers to study diseases like cancer, Alzheimer's, and cardiovascular diseases in a controlled environment. This can lead to a better understanding of disease mechanisms and the development of targeted therapies.

   According to the company, Organovo's bioprinting process starts with the identification of key architectural and compositional elements of a target tissue, and the creation of a design that can be utilized by a bioprinter to generate that tissue in the laboratory environment. The next step is to develop the bioprocess protocols required to generate the multi-cellular building blocks – also called bio-ink – from the cells that will be used to build the target tissue. While the bioprinting process is cell-agnostic, the company notes that its bioprinted tissues utilize primary human cells where possible in order to produce

the in vivo-like physiology most relevant for drug testing. Importantly, the company notes that it utilizes multiple independent sources for input cells to allow patient selection and high levels of diversity. The bio-ink building blocks are then dispensed from a bioprinter, using a layer-by-layer approach that is scaled for the target output. Proprietary biogels may be incorporated for temporary support or as filler to create channels or void spaces within tissues to mimic features of native tissue. The bioprinting process can be tailored to produce tissues in a variety of formats, including micro-scale tissues contained in standard multi-well tissue culture plates.

According to company researchers, most typically, hydrogels are deployed to create void spaces within specific locations in a 3D tissue or to aid in the deposition of specific cell types. This enables the company to employ a wide variety of proprietary cell- and hydrogel-based bio-inks in the fabrication of tissues. NovoGen Bioprinters also serve as important components of the company's tissue prototyping and manufacturing platform, as the printers are able to rapidly and precisely fabricate intricate small-scale tissue models for in vitro use as well as larger-scale tissues suitable for in vivo use. Generation of bio-ink comprising human cells is the first step in standard bioprinting. A wide variety of cells and cell-laden hydrogels can be formulated into bio-ink and bioprinted tissues, including cell lines, primary cells, and stem/progenitor cells. The majority of tissue designs employ two or more distinct varieties of bio-ink, usually comprised of cells that represent distinct compartments within a target tissue. In an example given by the company, a 3D liver tissue might consist of two to three distinct bio-inks that are each made from a single cell type, a combination of cell types, and/or a combination of primary cells and one or more bio-inert hydrogels that serve as physical supports for the bioprinted tissue during its maturation period, or to transiently occupy negative spaces in a tissue design.

As mentioned above, Organovo's technology has been used to create tissues from livers to kidneys and from bones to skeletal muscle, with many more tissues and tissues with varying conditions also having been created.

It's also important to note that the FDA has shown a willingness to consider the usefulness of 3-D technology and has approved a drug that is made using that technology—Spritam in 2015. In talks with management, we are pleased that the leaders of Organovo are in continuous contact with the FDA and working closely with them in taking the steps necessary to get treatments approved based at least partially on 3-D technology. Already, the company has worked with FDA to remove language in the agency's requirements that necessitated animal testing—certainly a nod toward the belief that 3-D technology can replace that former requirement in the approval process.

We mentioned in the introduction that the company is receiving royalty payments for the use of its bioprinting technology, and we believe that's an important part of the Organovo equation, but the primary focus will be on the development of inhouse drugs to treat a variety of conditions. To be a successful company, and to use the technology in all the exciting ways we believe it can be used, company management needs to focus on one treatment that it can get to market in the fastest manner and impact a sizable number of people. By doing this, the company will be able to start receiving more substantial revenue streams, which will allow Organovo to do more testing and create more solutions for a variety of diseases. According to discussions with management and company filings, the current understanding of intestinal tissue models and IBD models leads management to believe that the company has created models that provide greater insight into the biology of these diseases than are generally currently available.

THE SCIENTIFIC FOCUS

Inflammatory Bowel Disease (IBD) is a group of chronic inflammatory disorders that primarily affect the gastrointestinal tract. The two most common types of IBD are ulcerative colitis and Crohn's disease. These conditions are characterized by chronic inflammation of the digestive system and can lead to a range of symptoms and complications. Here's an overview of IBD, as well as descriptions of ulcerative colitis and Crohn's disease, along with their respective symptoms:

Inflammatory Bowel Disease (IBD):

- **Definition:** IBD is a term used to describe chronic inflammatory conditions of the gastrointestinal (GI) tract. It is an autoimmune disorder, meaning the immune system mistakenly attacks the healthy cells in the digestive system.

Symptoms of IBD:

1. **Abdominal Pain:** Persistent or recurrent abdominal pain, often in the lower abdomen, is a common symptom.
2. **Diarrhea:** Chronic and sometimes bloody diarrhea is a hallmark symptom of IBD.
3. **Weight Loss:** Unintended weight loss is common due to malabsorption of nutrients and loss of appetite.
4. **Fatigue:** IBD can cause fatigue and weakness due to inflammation and nutrient deficiencies.
5. **Rectal Bleeding:** Blood in the stool is a characteristic symptom of IBD, especially in ulcerative colitis.
6. **Frequent Bowel Movements:** Individuals with IBD may have a frequent urge to have bowel movements.
7. **Urgency:** A sense of urgency to have a bowel movement, often accompanied by an inability to control it (incontinence).
8. **Fever:** Inflammatory processes can lead to fever and other systemic symptoms.
9. **Loss of Appetite:** Reduced appetite and a feeling of fullness are common.
10. **Joint Pain:** Some people with IBD experience joint pain or inflammation.
11. **Skin and Eye Problems:** Skin rashes and eye inflammation can occur in some cases.

Ulcerative Colitis (UC):

- **Affected Area:** Ulcerative colitis primarily affects the colon and rectum.

- **Inflammation:** It causes continuous inflammation and ulceration of the innermost lining of the colon.

- **Symptoms:** The symptoms of UC include bloody diarrhea, abdominal cramps, and urgency to have a bowel movement.

Crohn's Disease:

- **Affected Area:** Crohn's disease can affect any part of the digestive tract, from the mouth to the anus, and can involve multiple segments of the GI tract.

- **Inflammation:** It is characterized by "skip lesions," meaning areas of inflammation are interspersed with healthy tissue.

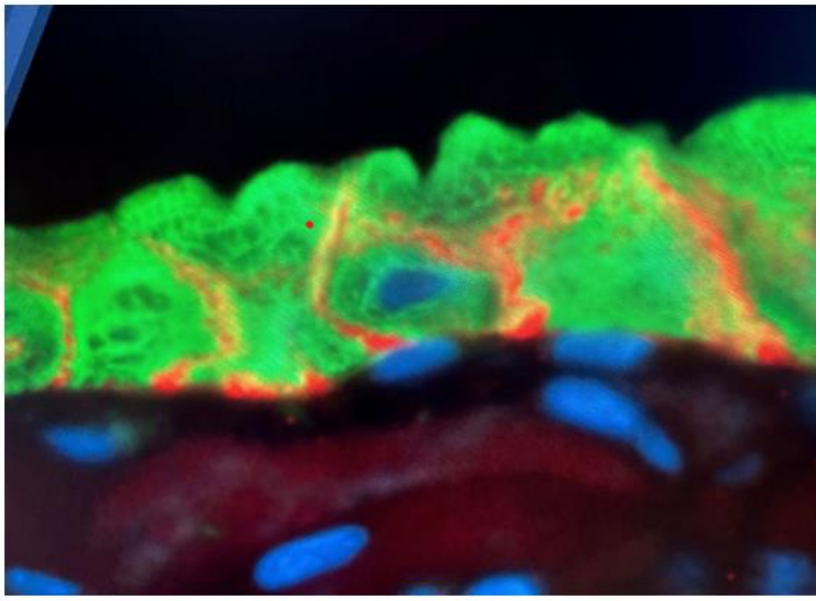
- **Symptoms:** The symptoms of Crohn's disease include abdominal pain, diarrhea (which may not be bloody), weight loss, and complications such as strictures (narrowing of the intestine), fistulas (abnormal connections between parts of the GI tract), and abscesses.

Both ulcerative colitis and Crohn's disease are chronic conditions, and their course can be unpredictable, with periods of remission followed by flare-ups. Diagnosis and management typically involve a combination of medical treatments (such as anti-inflammatory medications and immunosuppressants), lifestyle modifications, and, in some cases, surgery to address complications.

As mentioned above, the CDC estimates that over 3 million Americans suffer from some form of IBD and although there are existing treatments, Organovo is developing a treatment that we believe, and initial tests have shown the potential to be more effective and longer lasting. The simplified reason for this belief in layman's terms is that the FXR314 compound developed by Organovo is designed to treat the cause of the underlying condition, whereas other available treatments, including those seen incessantly advertised, treat the symptoms. And while treating the symptoms is important, we believe most patients would rather have symptom relief from the underlying cause being treated. Below is a pictorial

representation of that process that shows FXR314 treating the wall of the intestine (in green), with tight junctions (in orange):

The Wall of The Intestine Being Treated



Source: Organovo Holdings

To better understand how FXR314 works and why we believe it has the potential to be a superior treatment for IBD-related conditions, we must back up and delve deeper into the scientific explanation. If the detailed science is not of interest, readers can skip this section.

To begin with, the existing IBD treatments are known as antagonists. In the medical field, an antagonist refers to a type of drug or molecule that acts to counteract the effects of another substance in the body. These substances are often involved in various physiological processes, and antagonists are used therapeutically to treat diseases and medical conditions by blocking or inhibiting the actions of specific molecules or receptors.

Here's how antagonists work in the context of treating diseases:

1. Receptor Blockade: Many physiological processes in the body are regulated by the interaction between specific molecules (such as neurotransmitters, hormones, or growth factors) and their corresponding receptors on cells. Antagonists can bind to these receptors without activating them, effectively blocking the natural ligand (the substance that normally binds to the receptor) from binding. This prevents the receptor from initiating its usual response, thus altering the physiological effect.
2. Inhibition of Signal Transduction: Antagonists can also interfere with intracellular signaling pathways by preventing the transmission of signals initiated by the binding of a ligand to its receptor. By doing so, they can inhibit or dampen downstream cellular responses, which are often associated with diseases.
3. Competitive Binding: Some antagonists compete with the natural ligand for binding to the receptor. The antagonist has a higher affinity for the receptor, so it effectively outcompetes the ligand, reducing or blocking the receptor's activation.
4. Therapeutic Applications: Antagonists have a wide range of therapeutic applications. They can be used to treat various medical conditions, including:
    - Allergies: Antihistamines are antagonists that block the histamine receptors, reducing allergic reactions like sneezing and itching.
    - Hypertension: Beta-blockers are antagonists that block beta-adrenergic receptors, helping to lower blood pressure.

- Psychiatric Disorders: Antipsychotic medications often act as dopamine receptor antagonists, helping to manage symptoms of schizophrenia and bipolar disorder.
- Pain Management: Opioid receptor antagonists, such as naloxone, can reverse the effects of opioids and help treat opioid overdose.
- Cancer: Some cancer treatments involve the use of hormone receptor antagonists to block the growth-promoting effects of certain hormones on cancer cells.
- Autoimmune Diseases: Immune checkpoint inhibitors act as antagonists to block molecules that suppress the immune system, helping to enhance the body's immune response against cancer cells in certain cases.

Antagonists are valuable tools in medicine because they allow healthcare professionals to selectively modulate specific biological pathways and cellular responses. By interfering with the actions of target molecules or receptors, antagonists can help alleviate symptoms and manage diseases. However, their use attacks the symptoms of a condition rather than the cause and must be carefully controlled and monitored to avoid unwanted side effects or unintended consequences.

The newest antagonists being used in the treatment of IBD-related conditions are anti-TNF-alpha and anti-12/23 drugs. For the sake of brevity, we will use the latter term but acknowledge that it applies to both terms in each case mentioned below. The term "anti-12/23" typically refers to a specific class of biologic medications used in the treatment of autoimmune diseases, including colitis, particularly in the context IBD such as Crohn's disease and ulcerative colitis. These medications are more precisely known by names such as "anti-IL-12/23 antibodies" or "IL-12/23 inhibitors."

Here's an explanation of how anti-IL-12/23 antibodies are used to treat colitis:

1. Role of IL-12 and IL-23 in Inflammation:
- Interleukin-12 (IL-12) and interleukin-23 (IL-23) are cytokines, which are signaling proteins involved in the immune response.
- IL-12 and IL-23 play a role in regulating the immune system, particularly in promoting inflammation.
- In conditions like colitis and other autoimmune diseases, there is often an overactive immune response, leading to excessive inflammation in the gut.

2. Mechanism of Action of Anti-IL-12/23 Antibodies:
- Anti-IL-12/23 antibodies are biologic drugs designed to specifically target and block the effects of IL-12 and IL-23 in the body.
- By binding to these cytokines, these antibodies prevent them from activating immune cells and driving inflammation.

3. Use in Colitis Treatment:
- In the context of colitis, which includes ulcerative colitis and Crohn's disease, inflammation in the intestinal lining is a key feature.
- Anti-IL-12/23 antibodies are used to reduce inflammation and help manage the symptoms of colitis.
- These medications are typically reserved for patients with moderate to severe disease who have not responded well to other treatments or have experienced intolerable side effects from conventional therapies, such as corticosteroids or immunosuppressants.

4. Medications in this Class:
- There are several medications in the anti-IL-12/23 class, including ustekinumab, which is approved for use in the treatment of Crohn's disease and ulcerative colitis.
- Ustekinumab, for example, is administered as an intravenous infusion or subcutaneous injection and works by targeting both IL-12 and IL-23.

5. Efficacy and Considerations:
- Anti-IL-12/23 antibodies can be effective in inducing and maintaining remission in patients with colitis, reducing symptoms, and promoting healing of the intestinal lining.

- However, like many biologic medications, they can be associated with potential side effects, including an increased risk of infections, so their use should be carefully monitored by healthcare providers.
- The choice of treatment, including whether to use anti-IL-12/23 antibodies, depends on various factors, including the severity of the disease, patient preferences, and individual response to the medication.
  In contrast, Organovo's drug FXR314 is known as an agonist. In the medical field, the term "agonist" refers to a substance, typically a drug or a molecule, that binds to a specific receptor on a cell or in a tissue and activates that receptor. This activation often leads to a biological response or a series of physiological events. Agonists are a fundamental concept in pharmacology and are essential for understanding how drugs and signaling molecules interact with the body's receptors to produce specific effects.

Here are some key points to understand about agonists in the medical field:

1. **Receptor Activation:** Agonists are substances that mimic the effects of naturally occurring signaling molecules or neurotransmitters in the body. When an agonist binds to its target receptor, it triggers a cellular response that is typically associated with the natural ligand's actions.
2. **Types of Agonists:** There are two main types of agonists:
   - **Full Agonists:** These substances bind to a receptor and fully activate it, eliciting a maximal response.
   - **Partial Agonists:** Partial agonists also bind to a receptor but only activate it partially, resulting in a submaximal response. They may have a weaker effect compared to full agonists.
3. **Clinical Applications:** Agonists are widely used in medicine to modulate various physiological processes. For example:
   - **Pharmaceutical Drugs:** Many medications are agonists designed to target specific receptors to treat various medical conditions. For instance, beta-agonists are used to dilate airways in asthma, and opioid agonists are used for pain management.
   - **Hormone Replacement Therapy:** Hormone agonists are used to replace or supplement hormones in conditions like hormone deficiencies or hormonal imbalances.
   - **Neurotransmitter Modulation:** Agonists and antagonists are used to regulate neurotransmitter activity in the brain, which is important in the treatment of psychiatric disorders.
4. **Selective Agonists:** Some agonists are highly selective for a specific receptor subtype, while others may have affinity for multiple receptors. The selectivity of an agonist is important in minimizing unwanted side effects and maximizing therapeutic benefits.

Within the broad field of agonists, Organovo is specially working with an FXR agonist. An FXR agonist is a type of pharmaceutical compound or drug that activates the farnesoid X receptor (FXR), which is a nuclear receptor protein primarily found in the liver and intestine. FXR is a critical component of the regulatory network that controls various aspects of bile acid metabolism, lipid homeostasis, and glucose regulation in the body. FXR agonists, by binding to and activating FXR, modulate these biological processes and have potential therapeutic applications in several medical conditions. Here are some key points about FXR agonists:

1. **FXR Receptor:** The farnesoid X receptor (FXR) is a type of nuclear receptor, meaning it is located inside the cell nucleus and plays a role in gene regulation. FXR is primarily expressed in the liver and intestines, where it plays a central role in regulating bile acid synthesis, transport, and metabolism.
2. **Bile Acid Regulation:** FXR activation has a significant impact on bile acid homeostasis. When FXR is activated by an agonist, it leads to the suppression of bile acid synthesis in the liver and promotes the transport of bile acids from the intestines back to the liver, reducing their levels in the bloodstream.
3. **Lipid and Glucose Regulation:** FXR agonists also influence lipid and glucose metabolism. Activation of FXR can lead to improved insulin sensitivity, reduced triglyceride levels, and decreased fat accumulation in the liver, making FXR agonists a potential target for treating metabolic disorders like type 2 diabetes and non-alcoholic fatty liver disease (NAFLD).

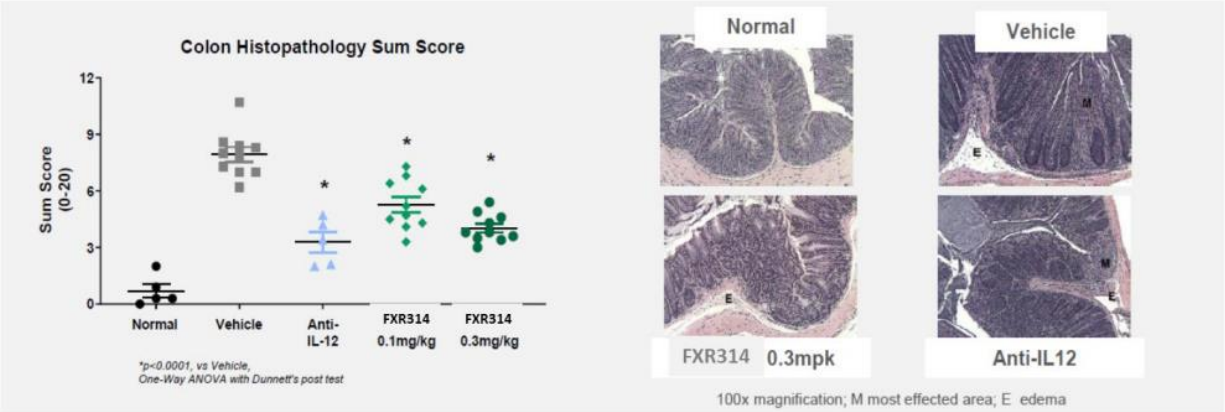
4. **Potential Therapeutic Applications:** FXR agonists are being investigated for their therapeutic potential in a range of medical conditions, including cholestatic liver diseases (conditions characterized by impaired bile flow), inflammatory bowel disease, and metabolic disorders. They are also of interest in research related to obesity, atherosclerosis, and certain types of cancer.

   In summary, an FXR agonist is a pharmaceutical compound that activates the farnesoid X receptor, a nuclear receptor protein involved in regulating bile acid metabolism, lipid homeostasis, and glucose regulation. These agonists have the potential to be used as therapeutic agents in various medical conditions.

   Activation of the farnesoid X receptor (FXR) can play a role in protecting the intestinal epithelial barrier integrity and function. The intestinal epithelial barrier, also known as the gut barrier, is a critical component of the gastrointestinal tract that separates the contents of the gut, including bacteria and toxins, from the bloodstream. Maintaining the integrity and proper function of this barrier is essential for preventing the development or exacerbation of various gastrointestinal disorders, including inflammatory bowel disease (IBD). Here's how an FXR agonist can contribute to protecting the intestinal epithelial barrier:

1. **Tight Junction Regulation:** FXR activation has been shown to influence the expression and localization of tight junction proteins, such as occludin and claudins, which are essential for sealing the gaps between adjacent epithelial cells. By enhancing the expression and assembly of these proteins, FXR agonists can strengthen the tight junctions, reducing the permeability of the epithelial barrier. This helps prevent the leakage of harmful substances, including bacteria and their products, into the underlying tissue and bloodstream.
2. **Mucin Production:** Mucins are large glycoproteins that form a protective layer on the luminal surface of the intestinal epithelium. This mucus layer acts as a physical barrier that traps bacteria and prevents direct contact between luminal contents and the epithelial cells. FXR activation has been associated with increased mucin production, which can enhance the protective barrier function of the mucus layer.
3. **Anti-Inflammatory Effects:** Chronic inflammation in the gut can compromise the integrity of the intestinal epithelial barrier. FXR agonists have been shown to have anti-inflammatory effects in the gut by reducing the production of pro-inflammatory cytokines and promoting the release of anti-inflammatory factors. This anti-inflammatory action can help preserve the structural and functional integrity of the barrier.
4. **Microbiota Modulation:** The gut microbiota plays a crucial role in maintaining gut health and barrier function. FXR activation can influence the composition of the gut microbiota by promoting the growth of beneficial bacteria that are associated with a healthy gut barrier. A balanced and diverse microbiota can contribute to barrier integrity.
5. **Bile Acid Regulation:** FXR is a key regulator of bile acid metabolism. Dysregulation of bile acids can impact gut barrier function. FXR agonists can modulate bile acid composition and transport in a way that promotes gut health and reduces bile acid-induced inflammation, which can contribute to barrier dysfunction.

   It's important to note that while the mechanisms described above suggest that FXR activation can help protect the intestinal epithelial barrier, the exact details of these processes and their interplay are still an active area of research that Organovo is pursuing at the present time. As seen in the figure below, the agonist treatment FXR314 has been shown to have a similar histopathology sum score as the current anti-12/23 treatments:

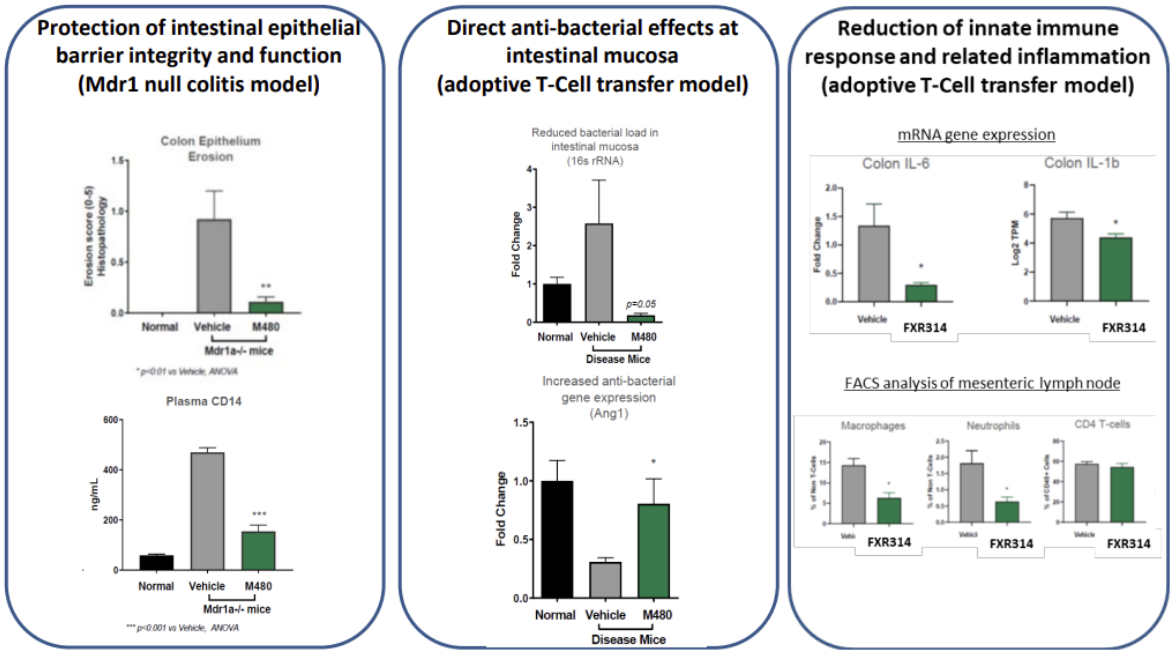


Source: Organovo Holdings

A histopathology sum score, often referred to simply as a "sum score," is a quantitative assessment used in histopathology to evaluate and summarize the pathological findings observed in tissue samples, typically from biopsies or surgical specimens. Histopathology involves the microscopic examination of tissues to identify and diagnose various diseases, such as cancer, inflammatory conditions, or infections. Sum scores are commonly employed in specific medical fields, such as oncology or rheumatology, to standardize and simplify the reporting of pathological findings.

The sum score is essentially a numerical representation of the severity or extent of certain histological features or characteristics observed in the tissue sample. The specific components of the sum score can vary depending on the disease or condition being evaluated, but for our purposes, we'll focus on the IBD case. In the case of Crohn's disease and ulcerative colitis, histopathology sum scores can be used to quantify the extent and severity of inflammation and tissue damage in colon or intestinal biopsies.
Sum scores are useful because they provide a standardized and objective way to communicate complex histological information among healthcare professionals and researchers. They help ensure consistency in the evaluation of tissue samples and can be valuable in tracking disease progression or treatment response over time.

Initial testing on the 3-D models with various conditions have also shown that the FXR agonist can move multiple readings of health much closer to the normal level:



Source: Organovo Holdings.

Given these positive results, the company recently announced that it has received a Study May Proceed letter from the FDA for a Phase 2 trial and plans on initiating enrollment in 2Q2024. Along with the announcement, CEO Keith Murphy noted that, ""Phase 1 safety data for FXR314, the data in our 3D human models of ulcerative colitis, and preclinical models all show very positive promise for FXR314 in the treatment of ulcerative colitis. We believe strongly that the fact that FXR314 is showing effects on disease in our 3D human cellular models of ulcerative colitis means that it has a greater likelihood of success in Phase 2 than a typical drug program. We are excited to be charting a path to clinical success in ulcerative colitis."

As investors, the main reason to be excited about the potential success of FXR314 in treating UC is the potential market size. The NIH (National Institute of Health) estimates that roughly 1 million Americans suffer from UC and cost Americans an estimated $2.7 billion last year.

In addition, given that FXR314 has shown so much impact on the epithelial barrier function, the drug may be able to prove that it can be used earlier than anti-TNF-alpha and anti-IL 12/23 drugs by treating physicians. The release of inflammatory cytokines happens a bit later in disease, so over time Organovo could demonstrate that FXR314 treatment can prevent the release of those cytokines entirely by keeping the epithelial barrier intact and preventing bacteria from penetrating the intestinal wall. Such an outcome would spell significant commercial upside, as it would potentially allow FXR314 to become first line treatment, or at the least an earlier treatment than current drugs that are already achieving billions in annual revenue in this patient population.

As you can see from the CEO's quotes and the potential market size, the company is focused on the IBD and UC markets in order to marshal its resources to the treatment that can get to the largest potential market in the quickest manner, and that's a major reason why we believe Organovo is on the road to success. However, the potential for future development is also quite intriguing and we wanted to highlight just one of the additional treatments in the pipeline that are presently intended for development through partnerships and show the future potential of Organovo.

NASH, or Nonalcoholic Steatohepatitis, is a progressive liver disease characterized by inflammation and damage to the liver, which is not caused by excessive alcohol consumption. Instead, it is associated with the accumulation of fat in the liver (steatosis) and inflammation. NASH is a more severe form of nonalcoholic fatty liver disease (NAFLD), where fat builds up in the liver but is not necessarily accompanied by inflammation or liver damage. Organovo's drug FXR314 has solid initial data and potential in NASH, but the company has said it is most likely to not pursue development in this area alone, but rather seek development partnerships.

Here's a detailed explanation of NASH:

1. Causes and Risk Factors:

- NASH typically occurs in individuals who have risk factors such as obesity, insulin resistance, type 2 diabetes, high cholesterol, or metabolic syndrome.
- It is believed to be related to an overaccumulation of fat in liver cells, which can trigger inflammation and cellular injury.

2. Pathophysiology:

- In NASH, fat accumulates within liver cells, leading to the formation of lipid droplets. This is often referred to as hepatic steatosis.
- Over time, the presence of excess fat can lead to cellular stress and injury, initiating an inflammatory response.
- Inflammation in the liver can further damage liver cells and may eventually progress to fibrosis, cirrhosis, and, in some cases, liver cancer.

3. Symptoms:

- NASH is often considered a "silent" disease because it may not cause noticeable symptoms in its early stages.

- As the disease progresses, individuals may experience symptoms such as fatigue, weakness, abdominal discomfort, and an enlarged liver.
- In advanced stages with significant liver damage, symptoms can include jaundice (yellowing of the skin and eyes), fluid accumulation in the abdomen (ascites), and confusion (hepatic encephalopathy).

4. Diagnosis:

- Diagnosis of NASH typically involves a combination of medical history, physical examination, blood tests, imaging studies (such as ultrasound or MRI), and sometimes a liver biopsy to assess the extent of liver damage and inflammation.
- Blood tests may show elevated liver enzyme levels and other markers of liver dysfunction.

5. Complications:

- NASH can progress to more severe liver conditions, including fibrosis (scarring of the liver), cirrhosis (advanced scarring), and liver cancer (hepatocellular carcinoma).
- Individuals with NASH are also at an increased risk of cardiovascular disease and may have associated metabolic conditions like obesity, type 2 diabetes, and high blood pressure.

6. Management and Treatment:

- Currently, there is no specific medication approved for the treatment of NASH. Management focuses on lifestyle changes and addressing underlying risk factors.
- Recommendations often include weight loss through diet and exercise, controlling diabetes and lipid levels, and avoiding alcohol.
- In some cases, healthcare providers may prescribe medications to manage related conditions or refer patients to specialized liver clinics for evaluation and management.

NASH is a growing concern worldwide due to the increasing prevalence of obesity and metabolic syndrome and provides a great future potential market for FXR314, which, as can be seen in the table below, has already shown positive test results in a Phase 2 trial:

Mean Change (BL to Week 16)	Placebo (N=20)	3 mg (N=21)	6 mg (N=20)
Median Liver Fat Reduction (MRI-PDFF) %	-1.5 %	-28.6 %	-26.9 %
% of patients with >30% Liver Fat Reduction (MRI-PDFF)	11.8 %	47.1 %	35.3 %
LDL-C %	-10.5%	4.5 %	19.4 %
Overall Pruritus Rate %	10.0 %	5.0 %	5.0 %
Pruritus-Related Treatment Discontinuation %	0.0 %	0.0 %	0.0 %

Source: Organovo

As we said, pursuing approval of FXR314 for NASH solely being considered as a partnering opportunity by Organovo, but we believe illustrates the potential Organovo has to grow into the future. The market opportunity for the NASH market is substantial from the numbers we have seen from the NIH (National Institute of Health). NASH is a form of NAFLD, as noted above, and the NIH estimates almost a quarter of Americans have NAFLD and roughly 5% of the population is suffering from NASH. Those numbers are expected to grow, with researchers estimating over half of US adults will have some form of NAFLD by 2040.

VALUATION

As readers of Zacks Research know, we are conservative in our valuations of companies, especially those at the clinical stage such as Organovo. There are inherent risks involved in companies at this stage of business but there are a few things that the company can do to reduce those potential risks and Organovo has done them. The company has a solid cash balance to finance operations, which is especially important at this time in the economic cycle, when credit is tightening. The almost $11 million on the company balance sheet as of June 30, 2023 should last them through at least the Phase 2 testing of FXR314 by our calculations and with no debt on the balance sheet the company has left itself in an excellent financial position in our view, leading us to assign a slightly lower discount rate of 20% to future cash flows than otherwise would be applied.

We then assume that the royalties the company is receiving continue at the current rate for the rest of 2023 and then grow modestly in the following years. We believe there is a good chance that Organovo will be able to extract sizable fees for use of its 3-D technology but for the purpose of valuation we are keeping our expectations modest. We also believe that FXR314 will first reach commercial status in 2026 and achieve a very modest 0.05% of the US UC market, which then grows at 10% per year for the foreseeable future. Note that we aren't assuming any additional approval, such as for use in NASH, but believe that there is a high likelihood of additional commercial products, leading to a potential upside to our estimates. Putting all of these assumptions together and we get to, what we believe is a conservative valuation of $12.15 per share. This represents a premium to recent prices but one we believe is justified by the potential upside to FXR314 and the other exciting developments that can come out using the company's 3-D technology.

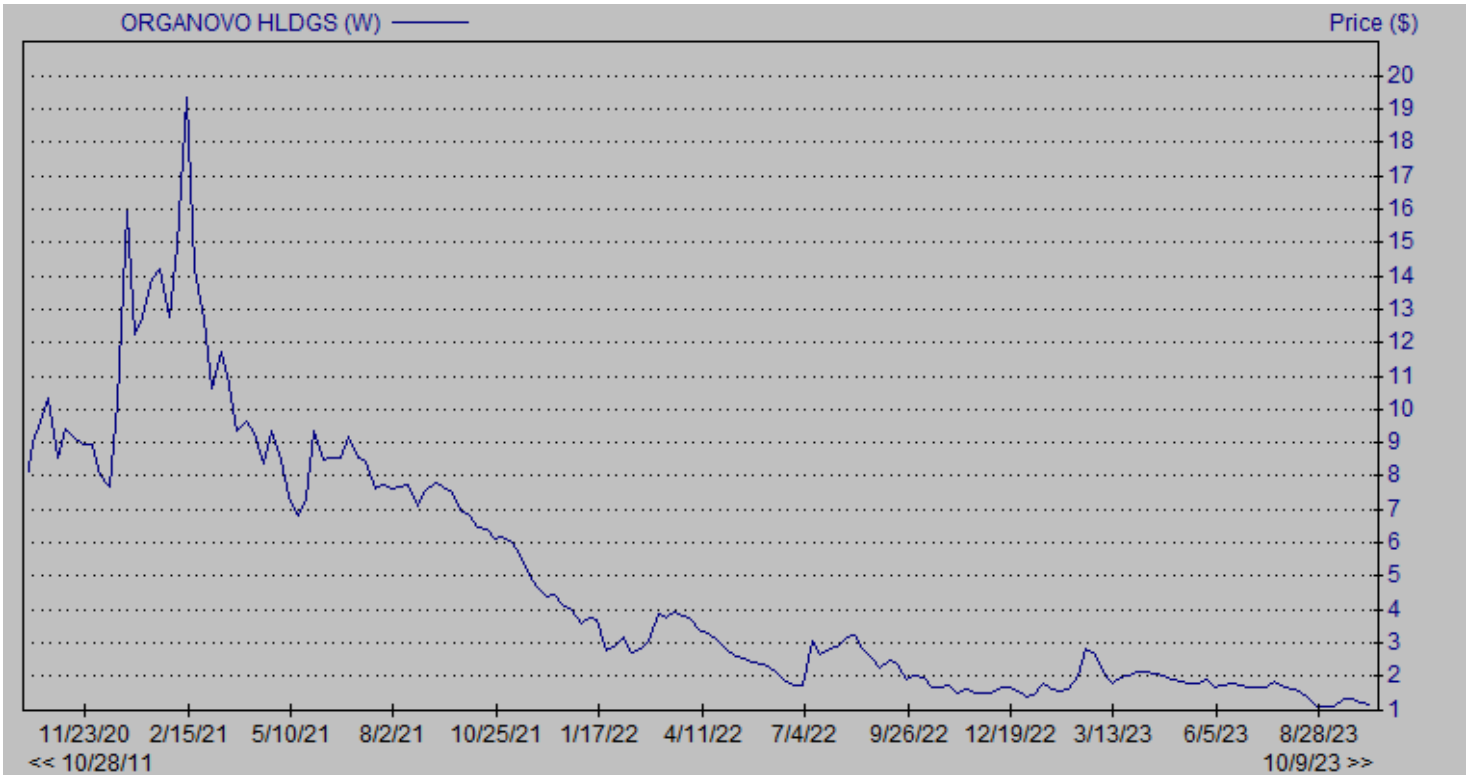
RISKS

- FXR314 could fail to gain regulatory approval.
- Competitors could come up with a similar product that evades the patent protection of MIRA but provides similar benefits as FXR314 potentially does.
- FXR314 has a small leadership team that we believe is vital to the potential success of MIRA. If one of those key leaders were to leave, it could prove difficult for the company to fill the gap in talent.
- Clinical stage companies often run into funding challenges and with credit conditions having tightened, funding could become a problem area for FXR314.
- The approval process through the FDA can be a volatile one and an unexpected bump in the road to approval could derail the goal of bringing FXR314 to the public.
- Doctors could be slow to add FXR314 to the treatment regimen they recommend for sufferers of the conditions treated by FXR314

PROJECTED INCOME STATEMENT & BALANCE SHEET

Organovo Holdings Income Statement and Balance Sheet							
(in thousands except for share data)							
March 31 Fiscal Year End							
	2022A	1Q2023A	2Q2023E	3Q2023E	4Q2023E	2024E	2025E
Revenue							
Royalty Revenue	370	75	75	75	75	444	533
Sales	0	0	0	0	0	0	0
Total Revenue	370	75	75	75	75	444	533
Research and Dev. Expense	8,885	1,666	1,683	1,699	1,716	9,063	9,244
Selling, general and admin. Expense	9,216	2,604	2,630	2,656	2,683	9,400	9,588
Total cost and expenses	18,101	4,270	4,313	4,356	4,399	18,463	18,832
Gain/(loss) from Operations	(17,731)	(4,195)	(4,238)	(4,281)	(4,324)	(18,019)	(18,299)
Other Income (Expense)							
Interest Income	454	157	456	457	458	459	460
Other Income (Expense)	20	12	20	20	20	20	20
Total Other Income (Expense)	474	169	476	477	478	479	480
Income Tax Expense	(2)	(2)	0	1	2	3	4
Net Gain (Loss)	(17,259)	(4,028)	(3,762)	(3,803)	(3,844)	(17,537)	(17,815)
Other Comprehensive income	2	0	4	5	6	7	8
Comprehensive gain (loss)	(17,257)	(4,028)	(3,758)	(3,798)	(3,838)	(17,530)	(17,807)
Gain/(loss) per share	($1.98)	($0.46)	($0.43)	($0.44)	($0.44)	($1.92)	($1.85)
Weighted Avg Shares of Common Stock	8,713,032	8,717,232	8,713,034	8,713,035	8,713,036	9,148,688	9,606,122
Assets							
Current Assets							
Cash and cash equivalents	15,301	10,754	10,969	11,188	11,412	11,640	11,873
Accounts Receivable	152	149	152	155	158	161	165
Other current assets	1,595	792	808	824	840	857	874
Total Current Assets	17,048	11,695	11,929	12,167	12,411	12,659	12,912
Fixed assets	902	850	859	867	876	885	893
Restricted cash	143	143	143	143	143	143	143
Operating lease right-of-use	1,705	1,606	1,526	1,449	1,377	1,308	1,243
Other assets	515	462	467	471	476	481	486
Total Assets	20,313	14,756	14,923	15,098	15,283	15,475	15,677
Liabilities and Stockholder Equity							
Current Liabilities							
Accounts Payable	331	488	498	508	518	528	539
Accrued Expenses	2,848	787	803	819	835	852	869
Operating Lease, current portion	492	495	505	515	525	536	547
Total Current Liabilities	3,671	1,770	1,805	1,842	1,878	1,916	1,954
Operating lease, net of current portion	1,313	1,210	1,315	1,316	1,317	1,318	1,319
Total Liabilities	4,984	2,980	3,120	3,158	3,195	3,234	3,273
Stockholder Equity							
Common Stock	9	9	9	9	9	9	9
Additional paid-in capital	340,317	340,792	340,317	340,317	340,317	340,317	340,317
Accumulated deficit	(324,998)	(329,026)	(328,524)	(328,387)	(328,239)	(328,086)	(327,923)
Other SE	1	1	1	1	1	1	1
Total Stockholders' Equity	15,329	11,776	11,803	11,940	12,088	12,241	12,404
Total Liabilities and SE Equity	20,313	14,756	14,923	15,098	15,283	15,475	15,677

HISTORICAL STOCK PRICE



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