INTEROFFICE MEMORANDUM

TO: JOHN MCCARTHY
FROM: MATT ARENS, FIRST LIGHT ASSET MANAGEMENT
SUBJECT: RESPONSES TO TWENTY GOOD QUESTIONS
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1. What is an area of health care public policy that is going in the right direction?

Access to health care. It is one of the rare instances in which numerous groups are joining forces with important constituents to try to make significant improvements. Of course, "access to care" is a broad term that applies to a variety of situations, but it principally refers to finding innovative ways to deliver effective health care to people who may be economically or geographically challenged, or elderly citizens who may not have easy access to transportation.

To address these challenges, both public and private payers are incentivizing greater access to care. Physicians who have long been aware of health care accessibility problems are robustly supporting these vital efforts. Additionally, the health care industry — primarily led by earlier-stage companies — is developing innovative products, services and business models that are enabling a level of access to care that previously was unattainable, which can create tremendous value for investors in those companies.

2. What is an area of health care innovation that is going in the right direction?

Precision diagnostics. For decades, it seemed most of the diagnostic industry was exclusively focused on test accuracy and reducing testing costs. While both of those objectives are critically important, there was little advancement around nor desire for companies that could drive diagnosis to a much deeper level. It's hard to blame the industry for this issue as diagnostic companies recognized there wasn't an appetite for reimbursing more expensive, higher-value-add testing.

This environment changed in a very meaningful way over the past ten years. The diagnostic industry has made a compelling case: if their tests can deliver actionable information enabling better outcomes for patients and eliminate other considerable costs, such as expensive therapies that may be ineffective, then these "expensive" tests can actually be cost-savers. As a result, a wave of diagnostic innovation is occurring that we believe will forever change health care and be critical to finding effective cures for many diseases.

3. If the consensus view is that small pharma is innovation and large pharma is distribution, how do you view this consensus?

I believe this consensus is both accurate and effective. In general, research and development productivity within large pharmaceutical companies has been declining for decades. This trend is not particularly surprising as we see it in other areas of technology development outside of the health care sector.

As pharmaceutical companies grow, their core competency typically shifts from innovation to competencies associated with efficiency, including greater effectiveness in areas such as sales and marketing, regulatory, reimbursement and intellectual property protection. When companies reach that point, it is a logical pivot to reduce spending on less effective research and development and allocate those dollars to mergers and acquisitions. This shift creates a symbiotic relationship between small pharma and large pharma benefiting both parties. Large pharma is able to acquire innovation to help drive growth, and small pharma benefits from the often meaningful premiums large companies pay for innovations that prove successful in the clinic.

4. What area of development stage biotechnology will we be hearing about soon, due to major advances?

Pulmonary medicine. Based solely on demographics, society was already on pace to need a greater number of more effective solutions for lung ailments, given chronic lung conditions increase both in prevalence and severity as we age. These needs likely will grow due to new or exacerbated lung diseases related to COVID.

Fortunately, there are innovative companies focused on developing solutions representing a range of treatments — from improving the standard-of-care to curing diseases at the genetic level. We are particularly excited about companies applying redosable gene therapy and those targeting previously “undruggable” targets that hold tremendous promise.

5. Is it true that virology was under-invested and under-attended until recently?

I think it is fair to say virology has been under-invested. Until recently, academia and industry largely avoided this area because the economic benefits of doing so were anything but clear cut. While virology is undeniably benefiting from increased attention due to the COVID pandemic, consistent interest and stable funding is required to meaningfully advance the science in order to adequately address both current and future virology challenges.

6. Biotech has a reputation of "binary outcomes" of success or failure. Assuming this is true, will this change, or is it part of the process?

I believe dedicated health care investors have done themselves a tremendous disservice by promoting what some refer to as a "golden era" of biotech investing. While increased knowledge and advancements in life science tools certainly provide greater opportunities to pursue better medicine, in our view, they do not broadly lead to fewer binary outcomes and higher batting averages, as some investors would argue. We believe the opposite is true — biotech will continue to feature binary outcomes and the probability of success for companies generally will be lower than it has been in the recent past.

This assertion is based on a couple of simple facts. The first is that every time a company advances a standard-of-care, the bar for success is raised. Second, although there's only been a slight increase in the number of diseases biotech companies are targeting, they are throwing many more agents at these diseases and they simply cannot all be successful. This reality is not nearly as big of a negative as it might seem. Biotech will continue to produce extraordinary winners that equity markets will tremendously reward. In this environment, it will be more difficult for investors to benefit from a broadly rising tide in biotech, and stock selection will be more critical than ever before.

7. What area of drug development offers good payoff in terms of relatively low cost and yet wide benefit potential?

Companies focused on addressing endocrine diseases provide a highly efficient development pathway as biomarkers measured from preclinical and early clinical trials are often used as regulatory endpoints in final pivotal studies, allowing for substantial de-risking early in development programs. This set-up is in contrast to some other drug development areas where early studies simply serve to identify safety characteristics across a range of heterogenous patients and dose levels; middle-stage studies attempt to identify the right type of patients and balance the risk/benefit scale; and late-stage pivotal studies attempt to leverage those learnings, but typically require completely different endpoints.

Drug development in the endocrine space also can be highly lucrative given a high unmet need, typically less competition than other indications, and advantageous pricing and marketing costs reflective of a smaller patient population. In addition, there are often commonalities across endocrine-based diseases, allowing different indications to respond to the same mechanism or agent. For example, the acromegaly and neuroendocrine tumor indications are both treated with SST2 peptide agonists, resulting in a more than $3 billion drug class for approximately 200,000 non-optimally treated patients.

8. Is Artificial Intelligence a game changer in drug discovery?

So far, artificial intelligence (AI) appears to be an important tool for companies to use in their drug discovery processes. Although, we have not seen anything that would indicate meaningfully better outcomes from the use of AI as compared to traditional methods. AI has certainly helped identify potential protein structures, and companies anticipate it will allow them to refine and reduce the molecules they test. However, the complexity of biology in a disease state cannot be underestimated.

To become a game-changing tool, an AI algorithm will need to understand not only how something works, but also how something does not work when in a diseased state, along with all of the specific ways it doesn't work, factors that influence it not working (genetics, social determinants, etc.), and ways the system may continue to fail even if the current problem is fixed (escape mechanisms and so forth). This task is a monumental one AI may someday be able to address, but it doesn't appear to be there quite yet.

9. You have much experience investing around orthopedics. What major themes or technologies are longer-term investable themes?

Much of the innovation in orthopedics and spine over the last 10-15 years has focused on creating new implants that improve upon traditional approaches to common procedures, including stemless shoulders, patient-specific knees, expandable interbody spinal cages and 3D-printed titanium implants. Moving forward, we believe two interrelated themes will contribute significantly to further enhancing orthopedic surgeries:

- Enabling technologies, including robotics, navigation/visualization equipment and pre-operative planning software
- New imaging modalities

These areas are receiving increased focus and investment as companies work to improve the consistency and outcomes of orthopedic procedures, with the long-term vision being the utilization of AI-based treatment planning software to fully design a surgical case. Among other capabilities, this software has the potential to leverage large amounts of data from past procedures to create 3D-printed, patient-specific implants and instruments, which are then paired with intraoperative navigation systems, allowing surgeons to implement a surgical plan with precision accuracy. This approach is a clear improvement on the current standard-of-care for many orthopedic procedures, which most often involve a surgeon determining the optimal treatment path during the operation itself.

The second theme centers on designing entirely new procedures to better treat orthopedic and spine conditions. Recent examples of this type of innovation include Alphatec's complete redesign of lateral spine surgery using its prone transpsoas (PTP) technique, which allows for lateral placement of interbody cages while a patient is in the prone position, and Treace Medical Concepts' Lapiplasty® procedure for bunion repair

rather than the standard osteotomy. In many cases, the implementation of these new procedures will rely on the enabling technologies discussed above.
Also, historically, orthopedic-related research and development has been focused, not surprisingly, on where the money is — hip replacements, knee replacements and spinal fusions. Going forward, the orthopedic areas which may see the most progress outside of hips and knees are the upper and lower extremities. These areas have not seen the same level of investment and attention from medical device companies, but that appears to be changing. Companies, such as Treace Medical and Paragon 28, are investing in the foot and ankle space, bringing new implants, procedures and technologies to patients. In fact, through its Smart28™ initiative, Paragon 28 is making large investments in enabling technologies for the foot and ankle market.

10. You also have experience in novel antibody development. What investable themes do you see there?

We continue to monitor the novel antibody landscape for truly transformational opportunities, though many are still early in their development. Technologies we monitor include:

- Antibody-drug-conjugate (ADC) approaches in which a chemotherapy-like toxin is attached (conjugated) to a target-seeking antibody in an effort to leverage the specificity of antibodies with the tumor-cell-killing potency of a toxin. There has been substantial progress made in developing this technology with multiple blockbuster ADCs on the market.
- Bispecific antibodies in which molecules are designed to recognize two different targets and create a novel action — such as T cell redirection and/or activation, targeting known tumor heterogeneity, targeting multiple checkpoints, and other novel functions. At their best, these agents appear to be able to provide efficacy approaching CAR T therapies, but with greater safety and without the infrastructure required that makes CAR T usage in the community setting challenging, if not impossible.
- Antibodies to deliver radioisotopes, as they are being increasingly explored after the recent approval of a therapy leveraging this technology in the prostate cancer space.
- Novel-but-early antibody technologies, including those leveraging masking technologies to only “activate” in the presence of a specific enzyme or tumor marker; antibodies built to respond to different pH levels in order to activate/de-activate in the presence of cancer cells; and technologies aiming to improve antibody shortcomings by altering peptides such that they mimic antibody binding characteristics while reducing the molecule size and time spent circulating to reduce adverse events.

We couldn’t be more excited about the opportunities antibody technologies will present over time. We will continue to closely monitor this space and anticipate it will lead to many exciting investments in the future.

11. What are the major differences investing in biotech in the USA and in Europe?

The two biggest differences we see between investing in biotech in the United States and Europe are the cost of doing business in those two geographies and the valuations generally afforded to companies. Europe enjoys a significant cost advantage when it comes to developing a drug. The cost of labor in drug development is extraordinarily high no matter where this development occurs. However, the cost of staffing a biotech company is significantly higher in the United States than anywhere else in the world. This meaningful cost advantage allows European companies to advance more projects than the United States, and sometimes allows a European biotech to take a more thorough approach to drug development where U.S. companies at times are forced into shortcuts. While costs differ materially between the United States and Europe, it is important to note both geographies are fortunate to have tremendous access to outstanding talent — a critical component of successful drug development.

The more significant difference between investing in biotech in the United States and Europe is the valuations generally afforded to companies. The valuation disparity does fluctuate, being greater during some periods than others. At First Light, we try to evaluate assets based on what we believe to be their intrinsic values, regardless of where those assets are being developed. As a result, from time to time, we find what we believe to be great investment opportunities in Europe where an asset has a lower valuation than what it might have if it were a U.S.-domiciled company.

There also are instances when a company may benefit by changing the geography of the exchange on which its equity is listed. For example, we've identified European companies listed on a European exchange that we believe may experience a step up in valuations if they would list on a U.S. exchange, such as the New York Stock Exchange or NASDAQ. Overall, our goal is to find attractive assets to which the market is not appropriately placing value, in our opinion, regardless of where those assets are listed. While we are primarily U.S. investors, we will take advantage of these arbitraged situations when they arise.

12. The amount of biotech IPOs has picked up meaningfully in the last few years. Significant change or passing phenomenon?

While the biotech funding cycle will wane as cycles have a tendency to do, we anticipate there will be a lasting effect from the sheer amount of capital deployed into the sector over the last few years. Many companies are going after the same indications and using the same mechanisms of action, which creates competitive challenges all along the commercialization path — from sourcing subjects in early stage clinical trials, to comparing datasets from a multitude of therapeutics to identify which ones might have the greatest potential to make it to market, to competing against countless other solutions to treat the same patients.

Throughout this process, most companies will need to continue to raise capital to fund their development, increasing the onus to show differentiation from peers or the next

wave of IPOs. While this situation creates a lot of noise in the short term, we believe companies with compelling data, a novel technology or unique targeted indications will continue to garner interest and funding, even in a more restrictive environment.

13. Regarding innovative medical devices, sometimes it takes years to achieve wide adaptation, and despite innovative acclaim, they lack commercial success. True?

Yes. You certainly can find several instances of exactly that progression playing out. However, I would argue that, in those instances, the lack of commercial success often is predictable. Many of those cases fall into one of two categories: the product was not truly solving a pressing health care need, or it was only a slight improvement on existing products. When we research a potential medical device investment at First Light, we frequently ask ourselves:

- Is this product answering a question no one is asking?
- Is this a "me too" product?

Medical devices can offer remarkable investment opportunities, but to be successful, one must thoroughly consider the product, the market, the reimbursement landscape and provider preferences. If all of these categories line up well, a medical device company that is able to remain independent long enough has the potential to deliver extraordinary returns.

14. Any areas of tech-enabled healthcare services that might offer a long-term theme?

There has been an explosion in the number of companies focused on leveraging technology to enhance patient outcomes and save the health care system money. Nearly all of them incorporate some degree of shifting the reimbursement model from "fee-for-service" to "value-based care," essentially putting providers on the hook for cost overruns above and beyond a contracted rate per patient. The approaches for accomplishing this goal range from simply providing software to acting as a fully integrated care provider. Many of these approaches have been attempted before with limited success, but reimbursement and regulatory momentum, along with improvements in technology and care routes, might make the current environment more favorable.

Outside of primary care, we remain excited about opportunities to leverage technology and related service models in hospital pharmacies where very complex and regulated processes, such as compounding medicines, can benefit from automation. This capability can help address labor issues and align core competencies with outside vendors within smaller hospitals that may struggle to successfully develop these abilities in-house. We see other service models being developed and successfully applied in areas, such as data analytics, where hospitals struggle to identify and hire top talent. Given the sheer amount of data health systems generate and the myriad of systems generating this data, we believe a conversion to enterprise-grade and cloud-based solutions and services is somewhat inevitable over the longer-term.

15. Since the human genome mapping in 2003, what have been a few of the more successful commercial areas stemming from this research?

Creating a reference human genome laid the groundwork for better understanding the genetic linkage to many diseases — both hereditary and non-hereditary. This knowledge has been leveraged by academic researchers, as well as drug development and diagnostic companies to create various therapeutics and products.

The oncology testing and therapeutics market has greatly benefited from discoveries linked to genomic markers. One of the most well-known examples was the identification of the BRCA1 and BRCA2 genes, which are linked to increased risks of developing breast cancer. This discovery led to the development of genetic tests that determine the likelihood that family members of cancer patients may develop the disease. Beyond hereditary applications, researchers have found other genes associated with cancers. For example, extra copies of the ERBB2 (HER2/neu) gene have been found in up to 20% of breast cancers. As a result, drugs have been developed to target this receptor.

While oncology has greatly benefited from insights resulting from a better understanding of our human biology, another major area of commercial success following the mapping of the genome has been prenatal testing. Today, routine testing for autosomal aneuploidy and trisomy has advanced to the point where physicians now primarily use a less-invasive approach via a blood draw, which is much safer than amniocentesis methods.

A commercial market also is beginning to emerge in pharmacogenomics, which utilizes the industry's understanding of drug-metabolizing enzymes to inform therapeutic dosing and reduce patient side effects. We expect this market to develop over time and other attractive opportunities to arise with origins stemming from our increased understanding of the genome.

16. Have FDA drug approval processes changed much in recent years?

The processes themselves have remained largely unchanged, but there is debate among companies and investors around whether or not the FDA recently has become more stringent. In select areas, the FDA does appear to be less accommodative than it once was likely due to changing leadership and potentially some controversial approvals. However, it's important to note that the burden on the FDA has increased substantially with the number of registered trials growing at a 14% compound annual growth rate over the past decade and the more recent impact of COVID, all without a commensurate increase in FDA funding or staffing levels. Overall, we believe an active drug with favorable efficacy and safety as proven by a well-run trial can be approved in this current environment. However, we and other investors will continue to closely monitor the pendulum that is the FDA to ensure it remains open to approving medicines that have proven they are safe and effective.

17. Any favorite quantitative screening metrics for initial positions?

Quantitative screening can be an effective tool and certainly has its place when evaluating most areas of the equity market. However, we believe it is a far less effective tool for identifying prospective investments within the portion of the market in which First Light invests.

Quantitative screening inputs frequently are incomplete or inaccurate for micro- and small-cap companies, often making outputs of limited value. In addition to insufficient data collection, other key data points crucial to the success of innovative health care enterprises, such as regulatory approvals or reimbursement decisions, typically are not available through screening.

Lastly, screening is unable to address major qualitative variables, such as the level of talent within an organization, particularly among the C-suite and board. In our experience, we have found the range of talent and capabilities among micro- and small-cap companies to vary widely and skew towards C-suites or boards with meaningful deficiencies in their abilities to understand The Street and/or the skills required to take a product or service through multiple stages of development. Because management execution is so crucial to the success or failure of smaller, innovative health care businesses, screening for quantitative factors, even valuations, generally proves to be of limited value.

18. Regarding portfolio position sizing, has your method changed over time?

We believe position sizing often is overlooked or underappreciated when analyzing an investment manager's effectiveness. From our perspective, a portfolio has the potential to be much more than a collection of stocks. At First Light, we spend a great deal of time considering the appropriate size of a particular position. We aim to ensure a position's size corresponds with the opportunity we believe an investment presents as measured by our intrinsic value calculation.

Investors often comment there is much more variance in the sizing of our positions compared to many of our peers, which is absolutely by design. We strongly believe there generally are only a handful of extraordinary investment opportunities available to us at any point in time — companies with such a significant skew of opportunity versus risk that they should be weighted several multiples above other attractive investments.

This belief, combined with our focus on smaller-capitalized stocks, is the single biggest factor behind our decision to significantly limit the assets under management (AUM) of our strategies. If we were to more equally weight positions within our portfolio, we could likely manage more than two times our target AUM. However, our internal analysis consistently demonstrates our returns would be meaningfully lower. Our method of position sizing has not changed over time and likely never will due to these important factors.

19. You focus on companies with less than $5 billion market cap. Does one need special skills in this area?

Given we primarily invest in small- to micro-cap health care companies, our investment team acutely focuses on the following areas when evaluating a company: management team capabilities, balance sheet status, the route to value-creating events, and potential risks given what can be a tremor for a large-cap company can feel like an earthquake to a micro-cap company. We consider a range of scenarios as part of our valuation process to account for the wider spectrum of outcomes typically at play for smaller-cap companies.

We generally are unable to leverage sell-side models in the way investors focused on larger-cap companies can. As a result, significant labor is required of our research analysts, which creates important proprietary content. Because smaller companies can perform so differently in a variety of market conditions, we believe extensive experience investing in this cap range truly is necessary for optimal performance.

20. You have been an Analyst and a Portfolio Manager. What are the major differences?

One of the biggest differences between an analyst and portfolio manager is accountability. When you are portfolio manager of a specific strategy, there truly is no one to blame for your mistakes. To be successful in that position, one has to own and be comfortable with this reality.

Another major difference between the two roles is the level of empowerment. Based on what I've seen throughout my career, analysts oftentimes feel their recommendations don't translate into portfolio holdings or their conviction around a certain name is not reflected in a particular position's weighting — despite the fact that analysts are tasked with having tremendous in-depth knowledge of their companies. This dynamic can lead to analyst burnout and/or animosity between an analyst and portfolio manager, which can meaningfully detract from performance.

Having spent many years in both of these roles, I implemented a slightly different model at First Light to reduce potential conflicts, empower our analysts and foster strong working relationships between analysts and portfolio managers. This model features "co-coverage" on all of our portfolio companies. Our senior research analysts are by far the most knowledgeable in our firm about the details surrounding investments within the subsectors they cover; they are the ones conducting laborious, critically important, meticulous analysis, including building comprehensive models.

At First Light, we layer on a second viewpoint to this analysis, which we believe is a significant advantage. This viewpoint flies at a higher level, looking across not only our entire portfolio but all health care subsectors to analyze and consider the interplay between them and how this may impact a portfolio holding. In my current role, I consider myself both an analyst and portfolio manager in that I oftentimes am involved in analyzing a holding from very early on in our research process through closing out the position. ###