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SOLUTION DEVELOPMENT
A Model For Structuring Biotechs And Developing Better Drugs

Industry must think differently about funding high-risk/reward development of drug candidates against novel targets. Multiplexed Phase II proof-of-concept trials can light a path toward lower-risk pivotal studies and provide a model for building biotechs to deliver what patients, providers, payors, and investors all want: solutions.

BY PETER KOLCHINSKY

- Current models of biotech drug development are inefficient and often fail to ask difficult questions at the proof-of-concept (POC) stage, resulting in inadequate de-risking and weak late-stage candidates.

- If a company were laser-focused on a single well-chosen indication and several of its best Phase I candidates were advanced together into the same Phase II program, the odds of overall POC success would be higher than for a typical single-drug Phase II study, and mediocre drugs that merely beat placebo but not other drugs would be less likely to get to market, sparing patients’ disappointment and investors’ capital.

- This Solution Development model offers a way of reconciling a company’s desire for diversification across multiple drug candidates with investors’ desire for a company to focus on its best program.

- Biotechs may be at the center of the Solution Development model, but there are intriguing roles for Big Pharma and non-profits in assembling drug candidates and incentivizing their developers in future multiplexed proof-of-concept trials.
he drug companies that have the hardest time raising capital to fund proof-of-concept research are the ones developing drugs against new targets. The irony is that in an industry that ostensibly strives to be innovative, investors hate risk and would prefer to invest in a reformulated (e.g., Alkermes PLC), repositioned (e.g., Cypress Bioscience Inc.), geographically relocated (e.g., Amaryllis Corp. PLC), re-launched (e.g., ViroPharma Inc.) or repriced drug (e.g., Questcor Pharmaceuticals Inc.) or enzyme replacement therapy NCE (e.g., Synageva BioPharma Corp.). These companies and others are successes in their own right but too exceptional to serve as role models for how our industry can continue to tackle large unmet health care needs in the coming decades. Such companies can raise money for a single validated agent; in fact, investors typically prefer that they focus on advancing one drug through later-stage trials and not divert any cash to an early-stage pipeline. (See “How To Create A Lasting Peace Between Biotech Management, Shareholders And Employees” — IN VIVO, July 2011.)

Yet it is likely that only innovative but riskier approaches can lift industry out of its current doldrums, providing the necessary advantages over current standards that will convince payors to agree to premium prices and generate the returns necessary for continued biotech investment.

One such path, described below, points to a new model of drug development and company building whereby biotech companies define themselves by the problem they aim to solve and not by the most advanced drug candidate in their pipeline. This Solution Development concept relies not simply on pulling together a stable of drug candidates in a particular therapeutic area, nor on building companies around other organizing principles like chemistry, technology platform, or type of drug target. Instead, it relies on assembling a set of candidates at the same or similar stage of development that address a specific, precisely defined indication and pitting those candidates against one another and a control in an unusual but powerful proof-of-concept study: the multiplexed Phase II trial.

Companies will typically take many molecules against the same target into animal models, move several through IND-enabling studies, and maybe even put a couple through Phase I. But once they embark on Phase II studies, the majority of biotech companies and even some smaller pharma will commit themselves to one particular drug candidate, even as the target problem morphs in response to an evolving standard of care, new market entrants, shifting regulatory hurdles, and reimbursement barriers. They don’t stop until a trial actually misses its endpoint (and even then many keep going thanks to non-prespecified analyses), the FDA rejects their candidate, or they wreck themselves trying to commercialize the product on their own, all based on little more than data suggesting the product is better than placebo.

If the bar for succeeding in Phase II is rising, then the odds of success of any one drug are likely to be lower than ever, especially when a company rises to the challenge by developing novel drug candidates against novel targets. It may be necessary to identify multiple active agents and combine them to get good enough efficacy to compete commercially. Novartis, for example, is taking this concept to the extreme by testing thousands of candidates in various combinations on hundreds of cancer cell lines to identify combination therapies suited not just to a particular cancer but to a genetically defined tumor or even multiple, genetic sub-populations of a single tumor. Most biotech companies, in comparison, are still flogging one drug.

One of the major causes for the high cost of drug development is that companies subject their drugs to very little negative selection before bringing them to market, merely demonstrating that they beat placebo in most cases, and therefore end up competing feverishly in the commercial setting where most discover that an FDA-approved drug isn’t necessarily “real-world approved.” Making drug candidates compete with one another through Phase II development will greatly improve the odds that the drug that comes out ahead is not just better than placebo but also comparatively better than other agents in terms of efficacy, safety, and convenience. In other words, better equipped to hack it in the real world.

The Solution Development model is also a way of reconciling a company’s desire for diversification across multiple drug candidates with investors’ desire for a company to focus on its best program. Before Phase II, when less is known about any one drug, the Solution Develop-
Exhibit 1

**In Diabetes Or In Non-Small Cell Lung Cancer, Many Companies Compete With A Single Candidate**

At least 48 different biopharmaceutical companies are pursuing clinical-stage treatments for type 2 diabetes. In non-small cell lung cancer, 41 different companies have drugs that are in Phase II or beyond. Only a handful of competitors – typically the largest companies – are pursuing multiple agents against the same disease. Here only the companies with the largest baskets of assets are identified.

**LEAKY INVESTMENT LOGIC**

Investing in biotech historically has been akin to betting that a plumber with one tool could fix a leak. Worse, some companies held themselves out to be all-in-one plumbers, piano tuners and electricians but came prepared only with three wrenches of different sizes. Imagine sending dozens of these under-equipped jacks-of-all-trades to plug a leak. What’s needed is for a plumber to show up with a well-stocked tool box.

In the prostate cancer space there are a variety of competitors on or close to market, each with only one agent. (See Exhibit 2.) Dozens of other companies are pursuing drugs in earlier development. In most cases, a company’s prostate cancer agent is just one of several programs it has in development for various disparate indications; in some cases the prostate cancer agent is its primary program and in other cases it is further down the pipeline. These companies are not running superiority studies against each other’s agents. They are trying to fit their drugs into a sequence, just after patients fail one standard-of-care agent and maybe in combination with another. If they all had their way, patients would go on 20 different drugs before being diagnosed with prostate cancer and death. That’s untenable unless most of those drugs are generic – and even then it’s far from desirable. Increasing the negative selection pressure on industry’s drug candidates at an earlier stage would vastly reduce the overall cost of drug development.
Exhibit 2
Prostate Cancer Drugs: Recently Approved Or In Late-Stage Development

Prostate cancer therapies in development don’t typically compete against one another … until they reach the market. Superiority studies in clinical trials would reduce this inefficiency and boost the winner’s chances of commercial success. Below is a list of recently approved agents and candidates in Phase III trials.

<table>
<thead>
<tr>
<th>Drug/Drug Candidate</th>
<th>Developer/Marketer</th>
<th>Development Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jevtana (cabazitaxel)</td>
<td>Sanofi</td>
<td>Marketed</td>
</tr>
<tr>
<td>Xgeva (denosumab)</td>
<td>Amgen</td>
<td>Marketed</td>
</tr>
<tr>
<td>Provenge (sipuleucel-T)</td>
<td>Dendreon</td>
<td>Marketed</td>
</tr>
<tr>
<td>Zytiga (abiraterone)</td>
<td>Johnson &amp; Johnson</td>
<td>Marketed</td>
</tr>
<tr>
<td>Enzalutamide (MDV3100)</td>
<td>Medivation/Astellas</td>
<td>Registration</td>
</tr>
<tr>
<td>Alpharadin (radium-223 chloride)</td>
<td>Algeta/Bayer</td>
<td>Phase III</td>
</tr>
<tr>
<td>Yervoy (ipiimumab)</td>
<td>Bristol-Myers Squibb Co.</td>
<td>Phase III</td>
</tr>
<tr>
<td>Orteronel (TAK-700)</td>
<td>Takeda/Millennium</td>
<td>Phase III</td>
</tr>
<tr>
<td>Custirsen (OGX-011)</td>
<td>Oncogenex/Teva</td>
<td>Phase III</td>
</tr>
<tr>
<td>Tasquinimod</td>
<td>Active Biotech</td>
<td>Phase III</td>
</tr>
<tr>
<td>Prostvac</td>
<td>Bavarian Nordic</td>
<td>Phase III</td>
</tr>
<tr>
<td>Cabozantinib</td>
<td>Exelixis</td>
<td>Phase III</td>
</tr>
</tbody>
</table>

SOURCE: Strategic Transactions; Company reports; clinicaltrials.gov

WHY INVESTORS PREFER SINGLE-INDICATION COMPANIES

Companies often have a hard time inspiring investors to back more than one program because it's difficult for two ambitions to co-exist in one pursuit. People tend to pick their favorites. There are many non-profits out there pursuing worthy causes, but each person is likely to favor only a few. If a non-profit were to tackle two causes and then go hunting for donors, it would find that a large percentage of those who like one cause don't like the other, making it harder to raise money than it would be for a non-profit focused on a single, compelling problem. The same principle applies to a company. Define yourself by the problem you aim to solve and identifying the people who will support you will be straightforward. If every problem had its own company, investors would find it easy to construct a portfolio of companies that perfectly represent their unique combination of priorities.

When a company does try to pursue drug development for more than one indication, investors generally focus on the most advanced and/or most valuable candidate and distill the company's valuation and identity down to that one program. If two or more candidates are both in Phase II trials, they will often look at the timing of proof-of-concept data, focus on whichever candidate will read out data first, and write off the other programs as merely "a pipeline." They assume that the company will sink or swim based on the outcome of the first program to yield major data. If that program fails, the company's valuation will plummet and investors will revisit the pipeline to see if there is anything of value; investors might then invest in the advancement of the next candidate at a lower valuation. If the lead program succeeds, the fate of the rest of the pipeline won't much matter. Either way, the pipeline is not relevant to the decision to invest ahead of the data readout from the first program.

Indeed, given the choice between a highly valued single drug and a pipeline/platform, the lead drug nearly always wins; in fact, if the lead drug hits a rough patch, often everything else is jettisoned, as illustrated by companies like Exelixis Inc. and Arena Pharmaceuticals Inc. (See "Exelixis Slashes Staff Again, Focuses All Internal Development on XL184" — "The Pink Sheet" DAILY, December 2, 2010.) And if the lead drug is successfully commercialized, then activist investors or acquirers often prevent management from trading very real cash flows "in the hand" for pipelines promises "in the bush," as many companies have discovered. Very few are entrusted with reinvesting cash flows from one drug into development of new drugs. The few exceptions usually are allowed to do so until they make a few mistakes, and then shareholders agitate for the cash to be returned through share buybacks, dividends, or sale of the company. Trusting biotech management teams with cash flow has not been a profitable strategy for investors, so they find it reassuring, once a company has a good candidate in hand, if the company is "built for sale" rather than "built to last," and that means no pipeline (with the exception of backup analogs to the primary asset).

Market forces conspire to make most companies channel limited resources to one purpose, making diversification across multiple indications and drugs challenging.

DIVERSIFICATION AND FOCUS, EACH AT THE RIGHT TIME

Just about the only companies in which a diversified pipeline is tolerated are those with early-stage candidates where investors do not know enough about any one candidate to channel the company in a particular direction. Of course, if the company is seen as unfocused, investors might not fund the company to go in any direction.
Defining the unmet need is the single most important thing that a company must do; an entrepreneur cannot escape his or her responsibility to define a worthy and appropriate problem, one that is both inspiring and tractable.

If all of a company’s drug candidates were laser-focused on a single well-chosen indication and were advanced together into the same Phase II program, then the odds of overall success would be higher and management could afford to focus only on its best candidate. According to drug development probabilities published by Tufts University’s Center for the Study of Drug Development, the average drug candidate has only a 30% chance of success in Phase II, which means a 70% chance of failure. Running a single multiplexed Phase II trial with three well-chosen candidates would therefore result in a 66% chance of at least one drug being successful (1 – 0.7^3), a dramatic improvement in clinical trial odds over a typical one-drug Phase II and therefore far more likely to be compelling to investors. Such probabilities are simplistic and certainly vary with the problem in question, but there are clear advantages to linking multiple, lower probabilities into a single, larger probability of a successful data readout.

The Solution Development model offers diversification across several innovative candidates in the pre-POC stage when so little is known about any one of them that to bet the company on just one would be too risky for most investors. Once a multiplexed Phase II trial is completed, investors and management would be aligned in wanting to focus further spending and development effort on the best candidate (any other candidate that beat placebo would be kept warm as a possible backup in case the lead stumbled later).

Of course, to start with, each of a Solution Development company’s candidates must be selected as carefully as if it was the one and only molecule the company had; diversifying across garbage will still result in failure akin to the housing subprime mortgage crisis. Therefore, a Solution Development company must not lower the bar for a drug candidate to qualify for a multiplexed Phase II. Likewise, investors and prospective partners must hold each drug to a reasonable standard of pre-Phase II validation; the drug must have demonstrated activity in a validated animal model, have showed good safety in animal studies, and have a high maximum tolerated dose with an acceptable dose-limiting toxicity profile. To reduce the chances of the drug candidates all falling for the same off-target or on-target toxicities, they would ideally have different chemical backbones and modulate different targets or even pathways.

The model also avoids a common problem associated with companies pursuing a “shots on goal” strategy: engineering data convergence on a single day spares the company and investors the roller-coaster ride of finding out which compounds failed and which succeeded at different points in time. (See sidebar, “Optimizing Behavioral Finance Theory.”)

**DEFINE THE PROBLEM, DEFINE THE RIGHT PATH**

Ideally, the only risk factors common to all the early-stage candidates would be the management team that selected them and the choice of indication, which are the essential elements of a Solution Development company’s identity. One might fear that the company chose the wrong indication, but if a management team cannot get that right, then it should expect to fail. Defining the unmet need is the single most important thing that a company must do; an entrepreneur cannot escape his or her responsibility to define a worthy and appropriate problem, one that is both inspiring and tractable.

Many companies form around all sorts of platform technologies, formulation science, drug targets, or therapeutic areas. They have perfectly specialized chemists or formulations experts or biologists. But these organizing principles often tear clinical teams in many different directions.

A company that truly specializes in spinal cord injury (SCI), for example, and that has three disparate ideas for how to spare spine trauma victims from becoming paralyzed, is more likely to succeed at its mission than a “neurology” company that is developing drugs for stroke, SCI, and seizures. Focusing on “neurology” is like a researcher focusing on “biology”; being successful requires a far greater degree of specialization in the disciplines involved in achieving an important goal. An SCI Solution Development company would likely have enough at stake in defining its objective carefully that its SCI-focused clinical team would have spent all its time optimizing the entry criteria for the ideal POC study and endpoints that would appeal to investigators, FDA, payors, ethicists, and, most importantly, patients. Unfortunately, like the hypothetical diversified “neurology” company, most ordinary biotech companies spread themselves thin, define themselves by anything other than a target indication, and end up effectively dabbling in each area into which they venture.

**INCHING TOWARD SOLUTION DEVELOPMENT**

It’s not easy to find examples of multiplexed Phase II trials, but the Solution Development concept is not new to pharma. In a COPD collaboration with Theravance Inc., GlaxoSmithKline PLC conducted a Phase II trial of two separate candidates (i.e., a two-plex Phase II), comparing one with the other and also with a control. The factorial trial, a close cousin of the multiplex trial, tests a combination drug against its separate components and a control, a strategy pursued by a variety of biotechs including Pharmasset, Vivos Inc. and Orexigen Therapeutics Inc. Eli Lilly & Co. and Roche have multiple drug candidates in each of diabetes and lung cancer and are therefore able not only to identify the best single agent of the group but also to experiment with combinations pre-commercialization. Pharmas are even partnering to combine their pipelines — or at least to test them in combination without sharing economics (e.g., Merck & Co. Inc./Roche in HCV, Merck/AstraZeneca PLC in oncology, GSK/Pfizer in HIV). (See Exhibit 3.) Unfortunately, anything resembling the Solution Development model is rarely deployed in biotech, but there are a few exceptions.
Large-scale Solution Development: Peer Dealmaking Among Big Pharma

Large pharmaceutical company peer deals to test individual assets in combination or to pair entire stretches of pipeline allow companies to share risk and increase their chances of commercial success. A few variations on peer dealmaking, described below, are likely to be emulated as larger companies grapple for models to improve R&D productivity.

<table>
<thead>
<tr>
<th>Deal</th>
<th>Date</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Merck/AstraZeneca combine early-stage oncology assets</td>
<td>June 2009</td>
<td>In what was considered a first of its kind collaboration, Merck and AZ agreed to research combining their respective candidates AZD6244 and MK2206 into one therapy for solid tumors. The companies will work together through Phase I testing and then consider future opportunities. Development costs are equally shared.</td>
</tr>
<tr>
<td>Pfizer and GSK form Viv Healthcare Joint Venture</td>
<td>November 2009</td>
<td>The two large pharmaceutical companies merged their HIV marketed products and commercial infrastructures to create Viv. The ownership stakes were determined by respective cash flows (and may be tweaked based on achievement of regulatory or sales milestones) and while individual pipeline assets remain the property of the originators, Viv covers certain expenses and retains options on those projects.</td>
</tr>
<tr>
<td>Roche/Merck study HCV combination therapies</td>
<td>May 2011</td>
<td>As part of a deal that includes a non-exclusive co-promotion agreement around Merck’s Victrelis (boceprevir) HCV protease inhibitor, Merck and Roche scientists will work on new and improved combination treatments using HCV agents from each partner’s portfolio.</td>
</tr>
<tr>
<td>Lilly/Boehringer team up in diabetes</td>
<td>January 2011</td>
<td>The drugmakers will develop and commercialize a portfolio of diabetes drugs in mid- to late-stage clinical trials. The program includes two oral diabetes drugs from BI, lixinaglitin, a DPP-4 inhibitor, and BI10773, an SGLT-2 inhibitor, and two basal insulin analogues from Lilly: the novel basal insulin LY2605541 and an insulin glargine product LY2963016.</td>
</tr>
</tbody>
</table>

Consider how Achillion Pharmaceuticals Inc. and Idenix Pharmaceuticals Inc. each have several anti-HCV drugs in early development. Recently, Achillion set aside one NS5A inhibitor that another company might have considered adequate, but management preferred a more potent one in its arsenal that would likely combine well with one of its two protease inhibitors. Pharmasset, recently acquired by Gilead Sciences Inc., had several HCV polymerase inhibitors and tested two nucleotides nearly in parallel; one did well and the other failed due to toxicity. Had Pharmasset’s two drugs been developed by two separate companies, there would have been one winner and one very pained loser; instead, there was just Pharmasset.

Vertex Pharmaceuticals Inc. was essentially the first HCV company to hit it big, enjoying a massive $3 to $5 billion valuation well before 2010, when other HCV companies started to come into their own. What kind of HCV company would Vertex be now if it had used its massive valuation to roll up diminutive peers like Pharmasset, Anadys, Inhibitex, Idenix and Achillion, aggregating whatever available drug candidates it might need to dominate HCV for the long run instead of simply being early to market with the one drug it had, telaprevir, which likely won’t be commercially relevant after 2014? Ultimately, Vertex did pick up a few additional assets and may yet retain an important role in the HCV space, but starting earlier with a Solution Development framework would have likely left Vertex far better positioned than it is today.

From among all indications, HCV may be an exception. It lends itself to faster and cheaper POC studies; early indicators of efficacy in Phase I are highly predictive of Phase II success. Furthermore, because of the size of the HCV market and rapid development timelines, pre-Phase II HCV companies today enjoy larger valuations relative to their capital requirements, resulting in a lower cost of capital, than companies in most other fields.

And although perhaps not intending to demonstrate a novel business model for others to emulate, Verastem Inc. may have been the first Solution Development start-up when it licensed in disparate early-stage compounds, all with activity in the same cancer stem cell model, and targeted them all at triple negative breast cancer. While none of the individual compounds offered much in the way of data, management inspired investors to fund development of three compounds up front all the way through a Phase II trial with PFS and survival endpoints. Atypically, that promise helped to raise $59 million in a successful January 2012 IPO. What happened next was possibly a more standard biotech play. In July 2012, Verastem licensed in a Phase II/III-ready FAK inhibitor from Pfizer and focused its efforts on starting a registration study in mesothelioma. Although the transaction made Verastem a later-stage company, the FAK inhibitor is likely to become investors’ sole focus, or will at the very least pull attention and funding away from the company’s multiple triple-negative breast cancer drug candidates.

An ongoing example of parallel development of multiple compounds for the same indications is Vertex’s CFTR corrector program for cystic fibrosis. Both VX-809 and VX-661 are in controlled POC studies, albeit separate ones, in combination with Vertex’s other CFTR drug, the potentiator Kalydeco (ivacaftor). Having so many compounds in development allows Vertex to experiment with combinations that would not be avail-
able to companies that put all their hopes on a single candidate. (See "Vertex's CF Therapy Combination Trial Yields Promising Lung-Function Data" — "The Pink Sheet" DAILY, May 7, 2012.)

THE POWER OF MULTIPLEXING

The Solution Development model and its primary clinical instrument, the multiplexed Phase II trial, offer a means for bringing better drugs to market more cost-effectively than we have in the past with greater buy-in from investors, physicians, patients, regulators, and payors.

Imagine a three-plex Phase II (three drug candidates) with two arms per agent to allow for different doses or dosing regimens (BID vs. QD) such that it had six active arms and one control arm. Such a trial would be better than a regular single-drug Phase II on many fronts with only a handful of manageable disadvantages, including cost, complexity and blinding.

It takes a lot of effort, time, and, therefore, money to design the right Phase II study. A three-plex Phase II would no doubt be more expensive and complicated than one that tested a single agent against placebo, but it wouldn’t be three times as expensive since not all clinical trial costs scale proportionately to a trial’s size. The greater investment of time/effort/money would actually result in less of each per compound, especially when taking into account the theoretically lower cost of capital for a company pursuing this design, given investors’ embrace of this greater chance of success.

This theoretical trial would also have advantages in patient recruitment. Patients do not want to enroll into a placebo-controlled trial. It takes a lot of effort for an investigator to explain to desperate patients that, if they want a chance of getting an experimental drug, they have to risk being randomized to a control arm. Letting placebo patients cross over to the experimental drug is sometimes one solution to convincing them to accept randomization to placebo, but this isn’t always possible, as in the case of survival studies, without confounding the endpoint analysis.

In the three-plexed Phase II with two doses of each drug and one control arm, patients might be inspired to participate by their greater likelihood of getting an experimental drug (six out of seven arms). Statisticians would point out that by using a single control arm for assessing the effectiveness of six experimental arms, there is a greater chance that an unusual placebo response rate in the control arm could simultaneously make all three drugs look too good or too bad. But even if the control arm were doubled in size so that it enrolled 25% of the patients, that still gives patients a 75% chance of getting an experimental agent, which are better odds than if the Phase II were testing two doses of a single agent versus placebo and therefore gave patients only a 67% of being in an experimental arm.

And not only do multiplexed trials offer greater probability of success, they also can increase the quality of a success with comparative effectiveness data; the winning drug will have been battle tested against not only placebo but also against other candidates. Multiplexed trials would result in drugs that are better vetted for competition in the commercial arena, where a drug has to be good enough for patients and payors, and not just good enough for statisticians.

If a three-plex Phase II showed that more than one agent were active, resources could be concentrated on advancing the best of them into Phase III development, improving the odds of commercial success and the return on investment (ROI). If the best drug then fails in Phase III trials, possibly due to toxicity, then the second best drug from three-plex Phase II would ascend to being best and might be a candidate for further development. Using adaptive trial designs, resources could even be shifted during the three-plex trial itself, moving patients away from drugs and doses that showed less promise. Were the multiplexed Phase II Solution Development model to be adopted.

OPTIMIZING BEHAVIORAL FINANCE THEORY

When a company attempts to interest investors in more than one development program, it subjects itself to a somewhat complex interplay between investors’ desire to have multiple shots on goal and their tendency to distill a company down to its lead program.

For example, Omeros Corp., PolyMedix Inc., and Tranzyme Inc. have been able to fund development of two agents almost in parallel. But it’s impossible to time the results of two independent parallel studies perfectly, and a public company can’t just sit on data while waiting for another trial to read out. As investors get closer to the data window for the two trials, they start betting on whether the first program will succeed or fail instead of looking at the overall odds of success of the two programs. Even if the trial results are only a few weeks apart, each day is an eternity as one gets down to the home stretch.

Many public funds are judged by their monthly performance and therefore hate to show even a paper loss. An aversion to the possibility of reporting a paper loss in the event of the first trial failing might prompt some investors to avoid the stock or sell it in advance of any data if they felt more comfortable with the second program’s chances of success than with those of the first. If the two programs were somehow perfectly synchronized and data were announced on the same day (only possible with a multiplexed trial), these same shareholders could hold the stock through the announcement knowing that they would be OK as long as at least one of the programs had good data.

The first of Omeros’ program to read out data was successful. But PolyMedix and Tranzyme were less fortunate and lost half their market values when their first programs failed. If either needed to raise much cash to get to data from the second program, that would have diluted shareholders significantly and potentially permanently impaired the long-term value of the stock price. But they have enough cash to get to the results of the second program and therefore may yet recover their investors’ paper losses.

In the case of a private company, it is not technically necessary to run a multiplexed Phase II for the purpose of engineering perfect data convergence. Since a private company’s stock is only repriced when it raises capital, a company only needs to ensure that multiple programs read out data before a financing is able to merge their chances of success into a single probability. But if it were to run a multiplexed Phase II program, then the private company could still enjoy all the other benefits of multiplexing addressed above as well as avoid the risk of one drug program getting significantly delayed relative to the others (from a behavioral finance standpoint, better they all get delayed together).