Valley Fever Solutions - Executive Summary

Overview

In the world of emerging superbugs, new treatment tools are critical. Superfungi have appeared already. The world has a strong need to look at additional antifungals, particular one with a novel MOA – mechanism of action. We plan to "kill two birds", and some dangerous fungi. Several companies are working to test new antifungals, in significant part to address these new fungi. None have our MOA. There is significant concern in the industry about these new fungi. No other drug has been demonstrated to be fungicidal against VF.

Our mission is to save lives, reducing the current 150 deaths a year from Valley Fever (VF), a terrible, painful disease that lasts for months, and often years. We are driving to secure approval for a new compound (NCE) with a novel mechanism of action that should dramatically improve the standard of care for VF. In reliable animal models, Nikkomycin-Z (NikZ) is fungicidal against VF (completely kills the VF infection), something no commercial drug or drug class can do. NikZ is synergistic against other fungi with very large clinical impact.

We are preparing to start a VF Phase 2a trial in early 2020. This delay is only because we are just finishing working out some API issues. We have started scale manufacture to make clinical trial scale drug substance (API) by late 2019.

With the unmet need to treat this orphan disease, addressing at least thousands of people who have no current therapeutic options, we anticipate a follow-on larger trial can be pivotal and support our goal of filing the NDA by 2021. Both of these trials should be dramatically inexpensive compared to typical drugs – approval for NikZ for only $35M from where we stand today. With financial support, we would like to follow the path of other orphan indications, combining the Phase 2a and pivotal trial in a single sequence.

We anticipate a peak market above $100M for VF alone. Additional applications, if they prove out, should increase revenue considerably. Most of the current standard of care drugs for VF had peak sales above $700M, one above $1B.

The safety profile of NikZ should drive the adoption faster than for a typical "me too" drug, and to patients on current therapies in addition to treating many patients with no current drug options. Orphan and QIDP designation give us 12 years market exclusivity. We are organizing new patent filings to provide an opportunity for expanded protection, and worldwide.

With NIH support, we are making trial material now, moving rapidly to multi kg scale after solving some challenging manufacturing issues. We seek $10-12M funding for a Phase 2a trial in subjects with established disease – the population most likely to benefit from our improved therapy. We are hoping for additional NIH support for substantial portion of this, augmenting the $7M in NIH funding we have received to date. With a 4-week and 4-month dual readout, and given the animal results, we expect favorable results within about 7-12 months of starting the trial. This should encourage partnering to run a larger trial, which could start in late 2020. That funding covers some needed additional pre-clinical testing needed before the trial.

We are collaborating with another group at NIH dealing with extremely ill patients. We are hoping to get information from testing NikZ in this population.

Valley Fever Solutions welcomes commercial support to drive NikZ quickly to approval.

The Indication – "Cocci" or "Valley Fever"

Coccidioidomycosis ("cocci," Valley Fever, "VF") annually infects 160,000 people, of whom about 60,000 become symptomatic. Many of these patients seek medical attention for their illness, resulting in some 9,000 hospitalizations for primary cocci, including some 2,000 for complicated cases. Many of these patients require medical monitoring for years, even for life, and 150 die. Many of the others are either misdiagnosed as having another type of lung infection or simply not diagnosed at all.

Some 2,000 suffer disseminated cocci, a particularly serious form of the disease. Roughly half of these do not respond to or cannot use the commercially available therapies. This last group is our initial focus for clinical trials.

About 22,000 cases are formally reported to the CDC each year. The natural incidence seems to be 2 to 3 times that, i.e. at least half of the cases are not detected in a way that gets formally reported. www.valleyfeversolutions.com. An Arizona state survey of newly reported infections found that illness lasted an average of 3 months and resulted in over a month of lost work.

Valley Fever is a major public health hazard in endemic areas. Some 6 million people are at risk each year in the primary endemic regions plus an additional 25 million in other endemic regions. More than 30,000 symptomatic cases (~ 60% of worldwide) occur annually in Arizona, mostly in the Phoenix area, accounting for a third of all community acquired pneumonia there. Another 6,000 cases (~10%) are seen in California's Central San Joaquin Valley (which is the origin of the "Valley" name of the disease).

Current treatments for Valley Fever still do not help a significant fraction of patients. In addition, patients frequently need to worry about relapses, even years later. Treatments of six to twelve months or more are not uncommon with the best available current drugs.

Nikkomycin Z (NikZ) is a new chemical entity (NCE), first in class new antifungal with a novel mechanism of action (MOA). NikZ is curative (fungicidal) in preclinical studies in established and reliable models for the disease. This would be a major advance if shown in humans since none of the currently available drugs do this. NikZ acts by blocking chitin synthase. Chitin is an important structural component of the fungal cell wall but is not found in animals. Thus, NikZ is very organism selective, with theoretically minimal to zero toxicity for humans or pets. All preclinical and phase I clinical studies support this. NikZ is significantly effective against other dimorphic fungi, particularly blastomycosis and histoplasmosis. NikZ potentiates other antifungals against other important diseases when co-administered with standard of care drugs. It may improve treatment of candidiasis and aspergillosis, particularly in immunosuppressed patients. These could lead to additional FDA-approved indications.

Market Opportunity

We expect annual revenue of >$100M for treating Valley Fever, likely about $135M and higher. This is based on the historical market size for fluconazole while on patent and on detailed marketing studies by the original NikZ IND sponsor. We have recently revisited this analysis – it remains in this range. If priced to match the current standard of care drugs for more serious cocci cases, revenue would be considerably higher. NikZ is fungicidal against VF, which is not true for any other current drug. We expect that alone will protect our unique niche. The high safety profile is likely to encourage some penetration into other VF prescriptions.

The market for systemic antifungal drugs was recently $6B according to recent reports, with historical and projected growth of 4% annually. Some reports are the market is $12B. Diflucan (fluconazole, the current standard of care for cocci treatment) sold $435MM in 2006 as an off-patent drug. For Diflucan while on patent, cocci patients spent about $2,500 for each moderate case, and much more for serious cases, often needed for years. Currently, each hospitalization costs about $50K per patient-visit sequence. Hospitalizations for VF in Arizona alone cost over $64 million in 2006. Recent data show hospitalization costs of $200M in Arizona and California to treat Valley Fever. Estimates of lost work earnings from patients easily exceed $100M annually. There is additional cost for caregivers, plus the emotional strain of disease.

Projecting one possible pricing structure, we anticipate NikZ revenue of $100-135 million per year for treating Valley Fever alone. The expected efficacy and minimal side effects will contrast sharply with existing therapies, driving rapid and thorough adoption. This is our initial and for now primary focus.

There is a good chance of a significant multiple in revenue from other indications such as candidiasis, aspergillosis, histoplasmosis and blastomycosis. This could easily reach >$500M total, given the $1.7B market for existing drugs used to treat cocci (among other fungi). Immunosuppressed or transplant surgery patients are at high risk of cocci and these other fungi, which can only help market adoption.

Even modest trial success would justify an effort to develop a chemical synthesis exploration effort, providing an entre into a drug discovery program of related compounds. Additional applications in

veterinary medicine should add about 10-20% in sales revenue. We have plans for a companion diagnostic, which could return modest additional revenue, plus drive primary sales.

Existing competing products include generics Amphotericin-B (in various commercial formulations) and diflucan (Fluconazole), and several other azoles. Some new antifungals are in various company pipelines, none yet approved. None of these have the MOA of NikZ, so far as we are aware.

Roadmap

Building on $7 million NIH and other funding to VFS, a further $3M from government grants and philanthropic sources spent at UA, and a $10M technology package from the original sponsor, the compound is ready to enter phase 2a clinical trial to assess its efficacy in humans. NikZ has FDA orphan drug designation for this indication. We should be a good candidate for $2M FDA support for clinical trials of NikZ as an orphan drug, following similar support in our Phase 1 trials.

We seek support for our "sweet spot" trial. New subjects would be selected from the population most in need of a solution – those with chronic, progressive cocci, many on track to take standard of care drugs for life unless our NikZ works as we hope. This trial would cost about $2.5M over 6-9 months, and likely will set up information sufficient to move to a pivotal trial. This trial would track the protocol of a 1997-2000 large scale NIH trial using two standard of care drugs, but this time with our new drug material. That older NIH trial was run by our John Galgiani, MD, 7 Nov. 2000 Ann. Int. Med. 676.

The medical community has a good understanding of the disease. Potential subjects should be relatively easy to identify and enroll in trials. One attractive sequence is: demonstrate NikZ is effective in seriously ill patients (GMP API availability + 6 months); demonstrate efficacy in moderately severe cases (API + 9 months) ("sweet spot trial"); expand trial for other cases (API + 15-18 months). This should set up what could be a pivotal trial, if thoughtfully designed. Of course a larger trial may be required, which could add a year or more. This relatively simple sequence might be achievable with funding modest in the context of typical trial costs. Total costs to approval could be as low as $30M and should not cost more than $50M if conducting two large trials.

In a bit more detail, we need to run some longer term animal toxicity studies. This will take 9-12 months at a cost of roughly $2M. We need some regulatory efforts, which we are organizing, which may end up costing $200K. This will include refining our trial protocol ideas and a meeting with the FDA to approve our plans. We need to choose a formulation shop, and engage them to turn our expected drug substance into oral dosage forms (capsules or tablets, about $1M to prepare methods, and to package some 30 kg API). Then we need to run the actual Phase 2a clinical trial. Our current design is expected to cost about $2.5-4M. This is a total of $10-12M for this proof of concept trial. With full funding, we would expect to complete the trial by mid 2020. We have proposals from multiple contractors with high experience in each of these aspects, so we can easily choose and execute efficiently.

This is a fairly compact roadmap. Positive proof of concept (expected) will drive a significant value inflection point. This sets up a larger, Phase 3 trial. This will be increasingly attractive to partners.

Funding history: Our 2010 $3M NIH "stimulus" grant supported development of a new manufacturing process, which we managed and proved at pilot scale of 500g per batch. We have bids to produce GMP product at multi kilogram scale. Finished drug product is expected to cost about $50/g (approximately a daily dose) and expected to drop rapidly to half that, then to $15/g with experience.

The FDA awarded a $1.5M grant in support of UA's VFCE's Phase 1 clinical trials for this orphan product. We anticipate similar additional FDA support may be granted to support Phase 2 and later trials.

We are considering strategic partners who are interested in accelerating our third objective – use of NikZ in immunosuppressed patients. This could lead to funding a full pre-clinical through Phase III sequence of approvals for serious cases.

Preclinical work in a few, very ill companion dogs is very encouraging. NikZ noticeably helped sick dogs, with 33 % completing the 3 month trial with resolution or near resolution of symptoms. We look to continue this review in some dogs to presage human trials. We could start that immediately upon funding.

We have plans to develop a more useful companion diagnostic that should provide critically needed early confirmation of disease, supporting appropriate treatment and early intervention. Such improved diagnosis could increase the market for NikZ.

Intellectual Property

Valley Fever Solutions has an exclusive license from the University of Arizona for Nikkomycin Z materials and clinical trial results, in addition to the original procedure for making NikZ. VFS has updated that manufacturing with new technologies and anticipates making NikZ more cheaply, and driving down costs over time. VFS is pursuing patents on our new manufacturing techniques. VFS expects protectable further development in taking the compound to market.

The University license to VFS includes VFCE's approved Orphan Drug Designation from the FDA, which provides seven years exclusive sales for the approved indication, which will be the only approved indication for NikZ. Orphan protection starts after the drug is approved, i.e. it covers all sales of Nik-Z for the first seven years of sales. This University license further includes the 2014 QIDP designation under the GAIN act, which confers an additional five years of market exclusivity, for a total of 12 years.

Management

Our virtual company looks small, but our record is strong. We have already managed to genetically re-engineer the basic Streptomyces strain, get to a producer strain, scale up manufacturing to 5-10% of full scale using full scale techniques, complete Phase 1 human trials, and secure $7M in NIH funding. This small team is enough to engage a CMO to make drug (we have already done this) and to engage a CRO to run a suitable human trial (we have done this before), this time to proof of concept Phase 2a data. We will continue to work with consultants and partners until we reach enough critical mass to begin hiring.

VFS was incorporated in October 2007, absorbing an earlier LLC formed in 2006 to support SBIR and STTR grant applications.

Our current board includes two people, chairman John Galgiani and director David Larwood. Our third director of many years has retired, for health reasons. Our grant supports three individuals, for a total of 0.8 FTE. David works more than 250 hours a month, and has for years.

Valley Fever Solutions' management team has extensive experience in the management of technology and the teams that develop it. They have worked together for over ten years, building on decades of experience in researching and treating Valley Fever.

- *David Larwood, MS, JD, MBA, President and Chief Executive Officer* –David took Verisity Ltd. public as its General Counsel and has since served as President of another startup and this one. His MS from UC San Francisco represents four years of a PhD program in Pharmaceutical Chemistry, where he helped invent a prominent drug delivery system (PEGylated liposomes, fundamental to Doxil, a major drug success). David has been leading our process development, including > 3,000 personal hours at the lab bench.
- *John Galgiani, M.D., Founder, Chairman*– John founded and has run the Valley Fever Center for Excellence at the University of Arizona College of Medicine since 1996, expanding on his decades of research into treatments, improved diagnostics, and vaccines for Valley Fever. www.vfce.arizona.edu . He is a leading clinical specialist for Valley Fever.
- *TBD Board Candidate* – Recent experience in commercial trials. Significant large pharma experience, some to considerable small to midsize pharma experience.

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We are a virtual company. David does much of his work from his home in Woodside, CA. Most of our manufacturing takes place in Midwest and New England states, and likely will involve OUS factories as we scale up. Clinical trials will be in areas of high infection – Phoenix, Tucson and Bakersfield, CA, where David grew up and where his parents lived for decades, until very recently.