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An Analysis of the December 2008 Arqule, Inc. and Daiichi Sankyo Co., Ltd. License, Co-Development and Co-Commercialization Agreement

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EXECUTIVE SUMMARY

In this transaction, ArQule and Daiichi Sankyo (DS) agreed to co-develop ARQ 197, ArQule's selective c-Met inhibitor, for the treatment and prevention human cancer indications and any other indications as agreed by the parties, in the United States, Europe, South America, and the rest of the world, but excluding Japan, China (including Hong Kong), South Korea, and Taiwan because ArQule had previously granted exclusive rights to Kyowa Hakko Kirin Co., Ltd. in those countries. ArQule and DS also entered into a separate Collaborative Research, Development and License Agreement dated November 7, 2008 utilizing ArQule's kinase inhibitory discovery platform to develop a new generation of highly selective, anti-cancer kinase inhibitors. In this white paper, we focus on the ARQ 197 License, Co-Development and Co-Commercialization Agreement.

Under the agreement, DS paid ArQule an upfront cash fee of $60 million and agreed to pay up to $560 million in development and sales milestones and tiered double-digit royalties on net sales of ARQ 197 by DS, its affiliates, and sublicensees. ArQule and DS are required to equally share the costs of Phase II and Phase III clinical studies, with ArQule's share of Phase III costs payable solely from milestone and royalty payments. DS is required to fund the costs of commercialization, and ArQule has an option to participate in the commercialization of ARQ 197 in the United States.

The financial terms of the deal were reasonable given the state of the economy in late 2008 and the amount of human efficacy data available at signing. The deal also increased ArQule's cash at a time when credit was tight. The deal with DS included a higher upfront than that of ArQule's 2007 deal for the Asian rights for ARQ 197 with Kyowa Hakko. The terms of the DS ArQule deal are comparable to other 2008 Phase II cancer deals with disclosed terms. The terms also are comparable (or higher) than the averages reported by Evaluate Pharma in its trend analysis for 2008 deals. However, in this deal, ArQule has to share in the development costs of Phase II and Phase III, reducing the true value to ArQule.

The overall structure of the transaction was well conceived and relatively straightforward. Sometimes partnering transactions can become overly complicated and, therefore, more susceptible to oversights in structuring and drafting the agreement. In this case, the parties successfully maintained a relatively straightforward structure and drafted a generally fair and balanced agreement with a number of particularly well worded provisions worthy of adaptation by business development professionals and attorneys for use in other deals.

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BACKGROUND

A Second Japanese Partner for ArQule?

DS, headquartered in Japan and ranked 21st in health care revenues worldwide with $8 billion in prescription and royalty revenues in 2008, was formed by the $15 billion merger of Daiichi and Sankyo in 2005. Sixty-three percent of its sales were in Japan and 21 percent in the United States, with Europe and India following. (DS also owns 63 percent of Ranbaxy Laboratories Limited, the Indian generic firm.) Cardiovascular products (angiogensin II antagonists , anti-lipid statin) accounted for 51 percent of sales, with oncology products constituting only 0.9 percent of sales according to Evaluate Pharma.

Recent news includes the July 10, 2009 FDA approval of Effient™ (prasugrel), an anti-platelet drug marketed with Eli Lilly & Company. In 2007, DS paid Amgen, Inc. $20 million upfront (and agreed to pay $150 million in development costs) for Japanese rights for denosumab, the bone metastasis and osteoporosis antibody. In 2008, DS acquired the cancer antibody company, U3 Pharma AG, for $234 million. In 2009, DS offered to acquire 20 percent of Zenotech Laboratories Limited, already 74-percent owned by Ranbaxy, but the offer has been delayed as minority shareholders have objected to the price.

ArQule, Inc., based in Massachusetts, is a public company with 107 employees and a market capitalization of $224 million as of September 23, 2009. ArQule began with a platform for small molecule lead optimization. ArQule is primarily focused on oncology, and its most advanced products, both in Phase II, are the c-Met inhibitor ARQ 197 (the subject of this deal) and the EF2 inhibitor, ARQ 501, partnered with Roche. In Phase I are an Alzheimer's drug candidate with Wyeth and an Eg5 kinesin inhibitor for cancer. In preclinical development are a b-raf program and a backup E2F inhibitor with Roche.

In 2007, Arqule granted Kyowa Hakko (now Kyowa Hakko Kirin) rights to ARQ-197 for Japan, South Korea, China, and Taiwan in exchange for $30 million in cash and up to $93 million in milestones, along with undisclosed sales milestones and double-digit royalties.

DS may not have seemed the most obvious partner for the European and U.S. rights to ArQule's ARQ 197 as ArQule had already partnered with a Japanese company for Asian rights. Presumably, at the time of negotiations, DS needed to persuade ArQule of its growing commitment to cancer, where it is currently a relatively minor player. DS likely touted that much (19/52 projects according to Evaluate Pharma) of its pipeline is now in oncology. It probably noted its July 2008 deal with Seattle Genetics, Inc. for antibody conjugates, its 2008 acquisition of the cancer antibody company, U3 Pharma, its 2007 deal with Amgen for denosumab for osteoporosis

and for bone metastases in cancer patients, its 2007 deal with Zenotech to market biosimilar GCSF to treat neutropenia in cancer patients, and its 2006 deal for YM Biosciences' antibody to EGFR for lung cancer. Also, DS could reasonably persuade ArQule that ARQ 197 would be a premier and advanced product in the DS oncology pipeline.

Given that the agreement excludes Japan, where DS makes 63 percent of its sales, it also is interesting to envision the discussions of how DS will maximize the product in other territories. In Europe, DS is a relatively minor player. Even in the United States, where DS makes about 21 percent of its sales, DS often is in co-promotion or joint ventures with large global players. One possibility is that DS will sublicense the drug for optimal commercialization, although ArQule's permission is required to do so for the United States. It is possible that ArQule saw significant value in the potential for a broader relationship with DS. At the same time as the agreement on ARQ 197, the two parties announced a research collaboration on allosteric kinase inhibitors, with DS paying ArQule $15 million upfront and paying two years of research support as well as potential license fees and milestones.

Finally, with these deal announcements, ArQule was able to deflect much attention from the decision by Roche in December 2008 to decline the option on ARQ 761, the second E2F inhibitor in its 2004 partnership with ArQule.

Overview of Transaction Structure

In this transaction, ArQule and DS agreed to co-develop ARQ 197 — as well as any agreed-upon backup c-Met inhibitor compounds[1] — in the United States, Europe, South America, and the rest of the world, but excluding Japan, China (including Hong Kong), South Korea, and Taiwan. ArQule retained an option to participate in the commercialization of ARQ 197 in the United States The parties agreed to collaborate on the clinical development of ARQ 197 as well as commercialization in the United States if ArQule exercises its co-commercialization option. DS is responsible for preparing and filing drug approval applications, manufacturing and supplying ARQ 197 active pharmaceutical ingredient and finished drug product, and commercialization activities, subject to ArQule's option to co-commercialize in the United States An overall joint steering committee will oversee development and commercialization of ARQ 197, and multiple additional committees that report to the joint steering committee will oversee specific aspects of the collaboration. ArQule's co-commercialization rights in the United States include the rights to co-detail the product, to provide a proportional number of scientific liaisons, to be

[1] While the agreement envisions the possibility for back-up c-Met inhibitor compounds, for ease of reference, the remainder of this white paper uses ARQ 197 to mean both ARQ 197 and any c-Met inhibitor back-up compounds agreed to be developed by the parties under the agreement.

displayed on marketing materials in equal prominence with DS and to receive training from DS prior to commencement of detailing.

Summary of Commercial Terms

DS paid ArQule an upfront cash fee of $60 million. Potential development and sales-based milestone payments total $560 million. ArQule also will receive tiered double-digit royalties on net sales of ARQ 197 by DS, its affiliates, and sublicensees. ArQule and DS are required to equally share the costs of Phase II and Phase III clinical studies, with ArQule's share of Phase III costs payable solely from milestone and royalty payments. DS is required to fund the costs of commercialization, and ArQule has an option to co-commercialize ARQ 197 in the United States. ArQule's milestone and royalty payments will remain the same in the event ArQule exercises its U.S. co-commercialization option.

ARQ 197, an Inhibitor of a Hot Target, at Phase I at Time of Deal

The target of ARQ 197 is the protein tyrosine kinase c-Met, which has been a target on the "hot list" for in-licensors. Many human cancers (including cancers of kidney, liver, stomach, breast, and brain) have constitutively increased c-Met activity, either through over-expression, activating mutations, or increases in the c-Met ligand, hepatocyte growth factor (HGF). Alterations in c-Met signaling have been implicated in tumor progression, angiogenesis, and metastasis.

ARQ 197 inhibits c-Met at an allosteric site not competitive to ATP, unlike most kinase inhibitors to date. It is likely to have a different profile than ATP competitive c-Met inhibitors that may share effects at kinases with similar active sites.

ARQ 197 is now in multiple Phase II trials. The first Phase II data has come from a trial in three relatively rare tumor types (clear cell sarcoma, alveolar soft part sarcoma, and Xp11.2-translocated renal cell carcinoma) sharing the feature of up-regulation of microphthalmia transcription factor (MiT), which is believed to upregulate c-Met. In these tough-to-treat tumors, out of 28 patients, one patient had a partial response and 17 had stable disease (ASCO 2009). These data were almost certainly not available at the time of negotiations of the DS ArQule deal.

ARQ-197 also is in Phase II for pancreatic cancer, another tough cancer that frequently has upregulated c-Met. A Phase I/II non-small-cell lung cancer (NSCLC) trial has dosing in combination with Tarceva® (erlotinib) because 25 percent of EGFR failures are attributed to c-Met gene amplification (Arqule presentation). In March 2009, a Phase II trial in hepatocellular carcinoma was initiated.

Significant c-Met Small Molecule and Antibody Competition (From PharmaProjects)

c-Met has been seen as an important target for cancer therapeutics with many tumors having alterations in c-Met signaling.

GlaxoSmithKline (GSK) exercised its option for a c-Met inhibitor GSK-089 (formerly XL-880) from Exelixis, now in Phase II in papillary renal cell carcinoma. Preliminary results from 20 evaluable patients included two patients with partial responses (ASCO 2009).

Bristol-Myers Squibb (BMS) partnered with Exelixis for XL184 (BMS-907351), a less-selective inhibitor of c-Met, Ret, and VEGFR kinases. GSK had previously declined to exercise its option for this molecule. XL84 is in a Phase III trial in medullary thyroid cancer patients, with completion expected in 2013; in a Phase Ib/II trial in NSCLC patients who had disease progression on Tarceva®; and in a Phase II trial in glioblastoma. BMS also has another c-Met inhibitor, BMS-777607, in a Phase I/II solid tumors trial.

In Phase I are small molecules from Merck, Amgen, Johnson & Johnson, Eisai, and Pfizer. MethylGene has a small molecule which hits a number of kinases, including c-Met in Phase I.

Roche (Genentech) has an antibody to c-Met in a Phase II trial in NSCLC in combination with Tarceva®. Schering-Plough partnered with AVEO for an antibody that binds the ligand, HGF, now in Phase I.

Analysis

Reasonable Financial Terms. The terms of the DS ArQule deal seem reasonable given the state of the economy and the relatively sparse human efficacy data available at signing. The deal also increased ArQule's cash at a time when credit was tight. The deal with DS had a higher upfront than that of ArQule's 2007 deal for the Asian rights for ARQ 197 with Kyowa Hakko. Kyowa Hakko paid $30 million upfront and a total of $123 million for the opportunity in Phase I. The terms of the DS ArQule deal are comparable to other 2008 Phase II cancer deals with disclosed terms. The terms also are comparable (or higher) than the averages ($36 million upfront and total of $193 million) reported by Evaluate Pharma in its trend analysis for 2008 deals. However, in this deal, ArQule has to share in the Phase II and Phase III development costs, reducing the true value to ArQule.

Licensor	Licensee	Date	Product	Stage at Signing	Up Front	Mile-stones	Equity Invest-ment	Royalties
ArQule	Daiichi Sankyo	Dec. 2008	ARQ 197 (c-Met)	Phase II	$60MM	Up to $560MM		Double-digit
Exelixis	BMS	Dec. 2008	XL184 (c-Met) and XL281 (b-raft)	Phase III, Phase I	$195 MM	Up to $150MM		Double-digit
Avant	Pfizer	April 2008	CDX-110, EGFRvIII vaccine	Phase II	$40MM	Up to $390MM	$10MM	Double-digit
Amgen	Takeda	Feb 2008	AMG 706 (KDR)	Phase II	$100 MM	Up to $175MM		Double-digit
Genentech (now Roche)	Biogen Idec	Oct. 2008	GA101, Ab to CD20	Phase I/II	$31.5 MM	Profit share		

DS was able to materially de-risk its investment in ARQ 197 by requiring ArQule to directly and equally share Phase II development costs and equally share in Phase III development costs out of milestone and royalty payments previously paid or payable in the future by DS. The deal is not structured as a profit-split to account for ArQule's obligation to share in development costs, so presumably ArQule was able to negotiate for higher royalties than it otherwise would have received had DS been responsible for all development costs.

DS is required to pay all commercialization costs, including ArQule's fully burdened commercialization costs in the event ArQule exercises its U.S. co-commercialization right, provided that ArQule's costs do not exceed DS' fully burdened costs of employing or otherwise engaging its own representatives who detail DS' oncology products in the United States. In addition, the agreement permits a proportional reduction of the ArQule costs to be paid by DS to the extent ArQule's sales force also details other products not covered by the collaboration.

ArQule's royalty share does not increase in the event it elects to co-commercialize ARQ 197 in the United States. Presumably, ArQule negotiated for the U.S. co-commercialization right because either it can leverage the sales force from its co-promotion with Roche for the E2F inhibitor ARQ 501, or build a sales force at DS' expense and under DS' tutelage, without needing to insist on requiring a higher revenue share from DS. Any co-commercialization by ArQule, however, will likely require additional indirect costs, particularly additional legal compliance costs. It is unclear from the agreement whether those additional indirect costs will be payable by DS.

Analysis of Agreement Terms

Committee Decisions. The parties carefully considered how to resolve disputes in the event the parties cannot unanimously agree at the committee level:

- DS has the final decision with respect to certain undisclosed matters
- ArQule has the final decision with respect to certain other undisclosed matters
- The parties will resort to arbitration with respect to some additional matters
- For certain decisions requiring unanimity, the parties have to find a way to agree without being permitted to resort to arbitration

Resorting to formal third-party arbitrators to decide matters of drug development or commercialization strategy may be problematic, but presumably the parties carefully identified those key strategic decisions as requiring unanimous approval or being within the final decision-making power of one party.

Commercial Supply. Under the agreement, DS has sole responsibility for manufacture and supply of ARQ 197 active pharmaceutical ingredient and finished drug product. ArQule successfully negotiated for the right to require DS to manufacture and supply ARQ 197 API and finished drug product for ArQule's third-party licensees and collaborators outside of DS' licensed territory pursuant to terms of a supply agreement to be negotiated by the parties in good faith. This requirement gives ArQule and Kyowa Hakko Kirin another potential source of supply for Kyowa's Asian territory.

Diligence. DS is obligated under the agreement to use commercially reasonable efforts to develop and commercialize ARQ 197 for all Targeted Indications in the Field and in the Territory. The agreement includes a useful definition of commercially reasonable efforts requiring the comparable efforts and resources as DS would use for similar-staged products with similar market potential. However, it is somewhat unclear what the parties meant by requiring commercially reasonable efforts for "all Targeted Indications in the Field and in the Territory." Targeted Indications are defined as *all* cancer indications as well as any other non-cancer indications the parties subsequently agree to include under the agreement. Given some other provisions in the agreement regarding "New Cancer Indications" (see ***Right to Conduct Additional Clinical Trials***, below), the parties probably meant that DS has to use commercially reasonable efforts to develop and commercialize ARQ 197 in those indications that the applicable committee decides to include in the global development plan. However, a strict reading of this provision would require DS to pursue all cancer indications. In addition, it is not clear whether DS' obligations would be satisfied if it pursues development and commercialization in only part of the territory, or even only one country in the territory. This question

could become important given DS' relatively small commercial presence in Europe. In some agreements, licensors specify that the licensee is required to use commercially reasonable efforts to purse regulatory approval for, and commercialize in, certain major market countries within the territory, so that a licensee is not obligated to pursue every country, but is obligated to pursue at least the major markets.

Data-Sharing With Other Collaborators. Sharing data generated by one collaborator with a licensor's other collaborators is a common issue in partnering transactions. The DS-ArQule agreement includes a useful structure to address this issue by providing that ArQule may share clinical information and regulatory filings generated by DS with any other licensees and collaborators, provided other licensees and collaborators have granted ArQule the reciprocal right to share clinical information and regulatory filings with DS. With respect to safety information, the agreement provides that at ArQule's request, DS and ArQule will meet with Kyowa to discuss information and coordination with respect to adverse event reporting and other safety matters.

Reimbursement of ArQule's Co-Commercialization Costs. As mentioned above, in the event ArQule exercises its right to co-commercialize ARQ 197 in the United States, DS is required to reimburse ArQule for its fully burdened cost incurred in conducting co-commercialization activities. The costs to be reimbursed may be no more than the fully burdened cost to DS of engaging its own representatives who detail DS' oncology products in the United States. Smaller companies often need to pay higher compensation to sales representatives and others in its commercial structure in order to attract top talent from Big Pharma. Therefore, this provision adds a measure of control over the co-commercialization costs DS will need to pay. The downside for DS is that in order to exercise its right to limit costs under this provision, it may need to disclose sensitive financial information regarding its own cost structure with respect to commercialization of other oncology products.

Right to Conduct Additional Clinical Trials. From time-to-time, one party in a collaboration may desire to conduct studies that are not approved by the other party, particularly with oncology products where there are a number of different tumor types that may be explored. This agreement contains a noteworthy provision allowing either party to conduct a clinical trial in a cancer indication that is not part of the jointly approved global development plan, at such party's sole expense.

The additional study may not be performed if the joint steering committee or designated senior officers of the parties determine that there is a substantial safety risk in the proposed clinical trial that is greater than the safety risk in other clinical trials of the same product being conducted by the parties for other cancer indications, or that there is a material risk of adversely affecting the label of the product for other cancer indications as a result of the proposed clinical trial. The agreement provides that this determination be made as a "joint decision," meaning

that if there is disagreement, the determination goes to arbitration under the dispute resolution mechanism. It is not entirely clear whether the party desiring to conduct an additional clinical trial would need to wait until conclusion of the arbitration proceeding if there is a disagreement as to safety or potential label impact. The agreement further provides for protocol review and comment by the other party and reimbursement of a portion of costs if the product receives regulatory approval in the United States, a major European country, or the EU for the additional indication. The right to conduct an additional clinical trial may only be exercised once every two years by each party.

Each Licensed Product. The development and regulatory milestones and sales milestones are payable for each licensed product, as opposed to payable one time regardless of how many licensed products achieve the milestones. The royalty tiers are similarly based on sales levels obtained for each product. When milestones are payable for each product or sales milestone tiers are separate for each product, it is often helpful to clarify when two products are to be considered the same product or different products. For example, the parties may want to clarify whether different dosage strengths, formulations, or therapeutic indications are considered the same product or different products. It is not clear whether the agreement includes this type of clarifying provision in the redacted text.

Generic Competition. Parties frequently negotiate for a reduced royalty rate in the event a product faces generic competition above a certain threshold in a particular jurisdiction. This agreement contains a well written generic competition provision, appropriately determining the threshold level of competition based on unit sales. The provision also includes a noteworthy feature in that once sales of the generic product reach a baseline level, a specific royalty rate reduction applies, and then if sales of the generic product reach a higher percentage of overall unit sales, a different, presumably larger, royalty rate reduction applies. The specific threshold sales levels and percentage royalty reductions were not disclosed in the redacted agreement.

License to ArQule Outside of the Territory. DS agreed to grant to ArQule a non-exclusive license to DS's intellectual property for use by ArQule in manufacturing, developing and commercializing ARQ 197 outside of DS's territory. Similar to the data sharing provision, ArQule is permitted to grant sublicenses under its license to DS intellectual property to third-party licensees and collaborators only if the other licensee or collaborator granted ArQule the reciprocal right to include its intellectual property in the license grant to DS.

Right to Sublicense in the United States. DS is not permitted to sublicense U.S. commercialization rights in the United States without ArQule's prior written consent. This ability to ensure DS is the commercializing party in the United States is particularly important for ArQule given its co-commercialization right.

ArQule's Rights Upon Termination. The agreement contains thorough provisions for ArQule's rights upon termination. In the event of termination, other than by DS for breach by, or insolvency of, ArQule, DS has the following obligations, among others:

- Assign to ArQule, free of charge, all product trademarks
- Assign or grant to ArQule an exclusive, worldwide, royalty-free license to all DS intellectual property rights specific to ARQ 197 and a non-exclusive, worldwide, royalty-free license under all other DS intellectual property necessary or useful to manufacture, develop and commercialize ARQ 197
- Transfer all regulatory filings to ArQule and provide all regulatory correspondence to ArQule
- Assign to ArQule all agreements for the manufacture of ARQ 197 or the conduct of clinical trials for ARQ 197, and cooperate with ArQule to obtain the consent to assignment for any agreements where assignment is prohibited
- Provide all inventory of ARQ 197 to ArQule
- If DS is the manufacturer, supply ArQule its requirements of ARQ 197 for a specific, but undisclosed, period of time at a price equal to DS's manufacturing cost for the first portion of that period, and at a cost-plus price for the rest of the period

In the event DS terminates the agreement for breach by, or insolvency of, ArQule, DS retains its license rights and payment obligations, but ArQule is required to pay for the license rights it receives under the agreement from DS in an amount to be negotiated in good faith by the parties.

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