Excelling Together for the Benefit of Women Suffering from Endometriosis
The Bayer-Evotec Strategic Alliance

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ABSTRACT

Despite an urgent medical need for novel treatments across a number of different diseases, the cost of bringing a new drug to the market has increased to an average of $2.6 billion. Projected returns on investment in research and development (R&D) for the top 12 Pharma companies have fallen to just 3.7% in 2017, from a high of 10.1% in 2010. In parallel, peak sales per product have continued to fall. They have now dropped 11.4% year-on-year since 2010, to an average of $394 million[1]. As a result of this development and the increasing economic pressure for novel drugs on the market, increasing R&D productivity is a key topic for any company to be successful in this space. Traditionally, Pharma companies perform most of their drug discovery activities in-house, while using contract-research organizations for certain defined service activities. Herein, we report on how, by building on complementary capabilities, a strategic partnership between Bayer, a large Pharma company and Evotec, an external innovation drug discovery and development company, enables novel treatment options for a rather neglected disease – endometriosis – in a highly productive manner. Over a period of 5 years and with an investment of about €90 million to date, within a performance based business model between Bayer and Evotec, six pre-clinical candidates were generated, three of which have initiated first-in-human clinical trials. The Bayer-Evotec alliance has delivered first-in-class science together with productivity improvements and has opened significant future opportunities for improved treatment options for women suffering with endometriosis.
Endometriosis is a hormonal and inflammatory disease in women, in which endometrial tissue grows outside of the endometrium. The condition often leads to severe, chronic abdominal pain resulting in problems during sexual intercourse, urination and defecation, and is also associated with subfertility. Furthermore, endometriosis has a significant, negative economic impact due to frequent sick days in many patients. The disease affects about ten percent of women of child-bearing age and is widely under-diagnosed, often up to ten years will pass between the onset of symptoms and diagnosis [2].

The current standard therapies for severe endometriosis are either highly invasive due to (often repeated) surgery, or prone to significant side effects due to the impact on the patient's hormone system by reducing estrogen levels and suppressing ovulation. Therefore, a high unmet medical need exists in this disease area, warranting the search for novel, effective and well-tolerated non-invasive treatment options.

A KEY DECISION BUILD, BUY OR PARTNER

With a strong heritage and market presence in Women's Healthcare and the significant medical need, Bayer identified endometriosis as an attractive research investment opportunity, specifically focusing on so-called “non-sex-hormonal” approaches, i.e., novel treatment options which do not interfere with sex-hormonal regulation or the ovarian cycle. The unmet medical need and the significant market opportunity created the requirement for work on a novel set of targets, e.g., in the areas of pain or inflammation, and access to assay technologies for which Bayer had limited in-house experience. To address these challenges, a decision needed to be made whether to build all the required capabilities and resources in-house, buy a research portfolio or look for a partner.

Due to the limited research activities in endometriosis globally at that time, buying a portfolio was not feasible. Building up in-house capabilities was seen as too time-consuming and resource intensive. Therefore, a search for a partner that had complementary capabilities and allowed for a jump-start of a joint portfolio was initiated.

The idea of building an endometriosis pipeline on the basis of a blend of fixed costs and variable costs was initiated by Bayer in early 2012.

PARTNER IDENTIFICATION

SWITCH FROM FIXED TO VARIABLE COSTS

In addition to having complementary capabilities, a specific focus was placed on identifying a partner with compatible ways of working. This could be summarized as ‘different enough to synergize, but similar enough to harmonize’.

The selection approach applied for this alliance at Bayer was based on a careful and systematic global partner identification process, considering technology platforms and available targets, but also considering business model and global footprint. As a result of this process Bayer identified Evotec as a partner fulfilling all the different criteria.

In October 2012 Bayer and Evotec have entered into a strategic research alliance with the goal of identifying three small molecule clinical candidates for the non-sex-hormonal treatment of endometriosis within 5 years. Under this agreement Bayer and Evotec have joint responsibility for early research and preclinical characterization of potential clinical candidates, with Bayer being responsible for the subsequent clinical development and commercialization. This approach has brought together two partners who are different enough to complement each other in order to create synergies, e.g., based on complementary technology platforms and capabilities, but similar enough to avoid disruptive intercultural and inter-organizational issues. One key argument for building the alliance was the build-up of a capital efficient structure which can optimally shift capacities between the two organizations in a “capital elasticity” driven way. Such an arrangement triggers the rapid scale-up of resources to follow good data, while the consequence of ambivalent data is the immediate stop-loss and re-prioritization amongst the portfolio of drug targets.

LIVING THE VISION CREATING A COLLABORATIVE CULTURE OF SUCCESS

When setting up and managing this alliance, a number of other specific principles were applied in order to maximize the probability of success. These concepts relate to focus
on projects that benefited from complementary capabilities, senior management engagement, alliance and project management, reward systems and culture and team spirit. Herein we outline these principles which we consider best practices for such a partnership and which have clearly contributed to the remarkable productivity by all industry standards of this collaboration.

**Complementary Capabilities and Portfolio Building Approach**

The alliance project portfolio was built based on early project ideas which originated either at Bayer, or at Evotec or jointly, thus ensuring that both partners are contributors and beneficiaries at the same time. Furthermore, for each project as well as for the entire portfolio the different capabilities of the two partners were combined to overcome scientific and technical hurdles quickly and jointly. Examples are given in Table 1. In order to build a comprehensive project portfolio which was capable of reaching the overall goals of the alliance, a joint and systematic target search was undertaken to generate new projects in addition to the ones initially brought in by each partner. Furthermore, a frontrunner plus follow-up project concept was implemented to ensure that the identified novel targets did not fail due to limited options based on a single compound class.

**Senior Management Engagement**

In order to ensure consistent and efficient joint decision making in an alliance setting it is crucial to develop a suitable governance structure and a trusting relationship between key decision makers on the various governance levels. This clearly includes senior leaders, who are ultimately responsible for making final decisions based on the working committee recommendations.

Having senior leaders of both partners involved early and deeply both in the partner selection and in the alliance preparation process, and therefore having developed a personal relationship with their counterparts early on, is an important success factor. The same senior leaders are now acting as “executive sponsors” on both sides, in order to facilitate conflict resolution and as senior ambassadors of the alliance within the partner organizations.

**Alliance and Project Management**

Efficient joint decision making, flexible resource management across multiple disciplines and steering of this complex multi-project multi-site collaboration is ensured through a well-organized three-level alliance governance structure, consisting of joint project teams (JPTs) directing and executing the scientific and technical work, a joint collaboration committee (JCC) managing the project portfolio, and a joint steering committee (JSC) overseeing the overall alliance. The JSC provides the link to key Bayer internal committees responsible for development decisions, and the transfer of information between the JCC and the JSC is ensured by the two alliance managers, who are members of both committees.

To ensure a focus on structure, process, mindset and culture, alliance management best practices such as alliance health checks and an alliance scorecard considering strategic, financial, relationship and operational goals were employed. In addition, a number of principles related to the reward model and to alliance team and individual motivation were applied to build a highly integrated and dedicated collaboration team.

**Reward Model**

The reward model is primarily based on success milestones and royalties, and therefore puts a strong emphasis on the sharing of both risk and reward. Under this model, Evotec received a €12 million upfront payment and with potential preclinical, clinical and sales milestones of up to €580 million, plus staged royalties.

This risk and reward sharing approach is further reinforced by a milestone system that was designed specifically to reward not only the success of individual projects, but also to heavily encourage the overall success of the collaboration. Accordingly, additional success milestone payments in addition to and exceeding the project-related milestones are due with a growing number of identified preclinical candidates, thus strongly encouraging the joint team to reach preclinical candidate status for multiple projects independent of their initial origin, and de-emphasizing any “not-invented-here” syndrome.

**Culture and Team Spirit**

Working in a partnership requires an extra effort by joint team members due to additional meetings and business travel. This is sometimes referred to as the “collaboration tax”, and this effect can lead to a lack of motivation of joint team members, up to the preference to rather work on non-collaboration projects. In order to address this issue,
a strong emphasis was put on setting up projects in a way that resources and capabilities at the partner are a crucial enabler for success, and also on providing individuals and teams recognition for joint success, resulting in increased motivation to “go the extra mile” within this collaboration.

As mentioned, the structure of the financial terms with a strong focus on success milestone payments outlined above has resulted in a high level of motivation of the joint collaboration team to make the overall alliance a success and has created a joint sense of ownership of the full project portfolio. Due to this innovative approach the alliance resembled a start-up company managing a portfolio of projects and resources, thus encouraging the early termination of assets not likely to deliver and dynamically focusing the available resources on the most promising projects.

In addition, joint conference attendance and collaboration team events have accelerated team building and the formation of personal relationships early on. Internal collaboration awards created specifically for this alliance have emphasized the importance of alliance success, and scientific staff exchanges have created a deeper understanding of each partner’s culture, while also contributing to individual team member recognition, thus ensuring a high level of dedication and buy-in.

PRODUCTIVITY IMPACT, MEASURES OF SUCCESS AND OUTCOME

Now that we have outlined the principles we have used to maximize the probability of success of this partnership, we would like to discuss the overall impact of the alliance, specifically the scientific impact, measures of success for the two partners, and deliverables and outcome.

Scientific Impact
Scientifically the alliance combines several fields of expertise, including drug discovery technologies, endometriosis disease biology, inflammation and pain. Both partners initially contributed complementary know-how relevant to the treatment of the disease, e.g., Evotec in the field of pain and Bayer in the area of inflammation and endometriosis, and working together over time have created not only a common knowledge base, but also the capabilities to address new scientific challenges, e.g., the development of sophisticated animal models. The mutual regular exchange of ideas and scientific know-how between Bayer and Evotec, open and honest discussion of challenges, and transparent goal and project portfolio tracking in the governance teams has been essential to building a world-leading early project portfolio in endometriosis research within a short timeframe.

Measures of Success
At Bayer, in addition to considering benefits like access to novel targets and technologies, research alliances are evaluated and compared based on their pipeline impact, i.e., the quality (based on the same criteria across different alliances), the number, and the (ideally continuous) flow of preclinical and clinical candidates that enter the pipeline. At Evotec, in addition to the opportunity to advance projects into clinical development, a solid flow of milestone payments is considered a success factor of alliances.

Deliverables and Outcome
Over a period of 5 years and with an investment of about €90 million to date six first-in-class/best-in-class non-hormonal preclinical candidates have been generated, three of which started first-in-human clinical trials already. The overall goal which was set at the beginning of the alliance was achieved in April 2018, when the third candidate entered the first-in-human clinical studies, after previous candidates had already been progressed to clinical development in August 2016 and July 2017. This clearly demonstrates the exceptional overall productivity of the alliance as well as the quality of the candidates, while meeting the goals and fulfilling the expectations of both partner organizations by delivering a continuous flow of project progressions for Bayer and milestone payments for Evotec.
CONCLUSION

Planning, building and executing a large research alliance is a complex and risky endeavor. However, we believe that by following certain systematic principles the probability of success of such partnerships can be significantly increased. These concepts we have outlined herein relate to partner identification, portfolio building approaches, senior management engagement, alliance and project management, reward models and team spirit. We consider these principles best practices for such a partnership as they have significantly contributed to the success of this research alliance. The push for a novel treatment in endometriosis within this comprehensive alliance framework clearly represents a role model for other areas of high unmet medical need where, through higher R&D efficiency, more shots on goal can be generated to improve pipeline output.
ACKNOWLEDGEMENT

We would like to thank all members of the Bayer-Evotec joint alliance team for their contributions and dedicated efforts.

Table 1: Examples of Complementary Capabilities

<table>
<thead>
<tr>
<th>Area</th>
<th>Bayer Contribution</th>
<th>Evotec Contribution</th>
<th>Joint Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Targets</td>
<td>Early endometriosis target pipeline</td>
<td>Targets from previous pain and inflammation programs</td>
<td>Solid starting project portfolio, supplemented by systematic joint target search</td>
</tr>
<tr>
<td>in vitro Assays</td>
<td>Ultra-high-throughput screening platform, 4.5m+ compound library</td>
<td>Target-specific secondary assay platform for candidate differentiation</td>
<td>Flexible assignment of assays to sites with most suitable technology</td>
</tr>
<tr>
<td>in vivo Models</td>
<td>Endometriosis model expertise, innovative spontaneous pain behavior readouts</td>
<td>Pain and inflammation model expertise, stimulated pain readouts</td>
<td>Joint development of inflammatory pain models relevant for endometriosis</td>
</tr>
</tbody>
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REFERENCES
