An industry update: the latest developments in therapeutic delivery

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This industry update covers the period from 1 September through 30 September 2017, and is based on information sourced from company press releases, scientific literature, patents and various news websites. The month saw the US FDA approve three new molecular entities, Aliqopa (copanlisib dihydrochloride) (Bayer Healthcare); Solosec (secnidazole) (Symbiomix Therapeutics) and Verzenio (abemaciclib) (Eli Lilly and Co). Intarcia Therapeutics Inc. has its application for approval of a novel drug device combination of exenatide for the treatment of diabetes rejected by FDA but said that it will work to address the concerns and refile the application. The impact of biosimilars in the market is steadily increasing with seven biosimilars approved in the USA and Sandoz hoping to add to this with its announcement that FDA has accepted its Biologics License Application for a biosimilar version of Roche's Rituxan. Circassia announced positive top line results of a respiratory drug, Duaklir (for the treatment of chronic obstructive pulmonary disease) and Sarepta (for its new treatment for Duchenne muscular dystrophy). Axovant Sciences Ltd announced the failure of its drug Intepirdine in the treatment of Alzheimer's, adding to a growing list of drug failures in this area. There were a number of developments in the area of oncology with Bristol-Myers Squibb and Infinity Pharmaceuticals announcing an expansion of their collaboration looking at combination treatments, as well as Eli Lilly and Co's approval for Verzenio. Rani Therapeutics and Intra-Cellular Therapies announced successful funding rounds to support their drug programs. Allergan announced a novel licensing deal for its dry eye drug, Restasis, which it hopes would allow it to stave off patent challenges from several companies looking to develop generic versions of the drug. New research suggests that loss of sense of smell can be linked to an increased risk of developing Parkinson's disease.

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Drug delivery & digital health technology

Propeller Health

Propeller Health (WI, USA) who over the past few years has forged several deals with pharmaceutical companies, in respiratory medicine (e.g., GSK and Novartis), to provide sensors that monitor inhaler use, announced an initiative to provide information on local asthma conditions. It is launching a service called Air, which uses machine learning to analyze anonymized asthma-related data in order to predict the risk of asthma attacks by geographical location. The system provides an application programming interface that allows individuals and organizations to access the data that they can then freely utilize in their own apps and services.

It has been a long-stated ambition of the company to provide technology that can warn sufferers of respiratory diseases to an increased risk of an attack, so that they can proactively adapt their behavior and medication plans to address this.

As its technology is being rolled out by many of the leading pharmaceutical companies active in respiratory disease, Propeller is creating the broader user base required to gather reliable data to make rapid predictions of changing conditions [1].

Business news

Novartis

Swiss pharmaceuticals group Novartis (VTX: NOVN; Basel, Switzerland) announced the appointment of Vas Narasimhan, as its chief executive designate, to succeed Joe Jimenez, who announced his intention to retire from the company [2]. Dr Narasimhan is currently the Global Head of Drug Development and Chief Medical Officer at Novartis and has been with the company since 2005. He is a medical doctor by training, receiving his medical degree from Harvard Medical School (MA, USA) and also obtaining a master's degree in public policy from Harvard's John F Kennedy School of Government (MA, USA).

Joe Jimenez will stand down as CEO on 31 January 2018 after more than 10 years in the company and 7 years as CEO. He stands down at an exciting time for the business with Kymriah, its CAR-T treatment for pediatric acute lymphoblastic leukemia, receiving early approval from the the US FDA; a key responsibility for Narasimhan will be to ensure the commercial potential of this drug for the business is realized.

But there are also challenges for the business that Narasimhan will have to address such as the future of its poorly performing Alcon business (which many analysts expect it to dispose of) and falling sales at Novartis' generics arm Sandoz, due to price pressure and delays in approvals of its growing biosimilar portfolio.

Following rapid global expansion under his predecessor Daniel Vasella, Jimenez focused on restructuring and streamlining the company and under his leadership, the company's share price has increased by around 50%. However, it has faced a difficult past for 2 years, with a decline in share price of around 20% followed by disappointing initial sales from a new heart drug, Entresto, which have improved but are still well short of the predicted \$3B anticipated peak sales.

Jimenez who came to Novartis from HJ Heinz, initially to lead Novartis's consumer business, is widely seen as the leader among big pharma companies on digital health, and has established a number of deals for the business with leading digital companies including Google and its smart contact lens and Qualcomm around the remote collection of patient data in clinical trials and a next generation connected version of Breezhaler that will be used to deliver a number of respiratory products.

Collaborations

Infinity Pharmaceuticals & Bristol-Myers Squibb

Infinity Pharmaceuticals, Inc. (NASDAQ: INFI) announced an expansion of its existing clinical collaboration with Bristol-Myers Squibb (BMS) (NYSE: BMY; NY, USA) evaluating the use of its investigational drug IPI-549 in combination with BMS's-approved drug Opdivo for the treatment of breast cancer [3].

This follows a previous announcement of the collaboration in November 2016. Opdivo is a PD-1 immune checkpoint inhibitor designed to overcome immune suppression and initially gained approval in 2014 for the treatment of advanced melanoma and since then for several other oncology indications. Preclinical data have demonstrated that M2, or protumor, macrophages are associated with resistance to checkpoint inhibitor monotherapy, such as Opdivo. Phosphatidylinositol-4,5-bisphosphate 3-kinase (PI3K-gamma) is highly expressed in tumor-associated macrophages. Inhibition of PI3K-gamma by treatment with IPI-549 results in reprogramming macrophages making the tumor more susceptible to targeting by checkpoint inhibitors.

BMS has recently announced several deals that build upon its expertise in Immuno-Oncology. These include a deal with Halozyme to use its ENHANZE[®] drug-delivery technology to support the delivery of BMS's oncology by subcutaneous injection; a collaboration with AbbVie to look at the use of ABBV-399 in conjunction with Opdivo to treat solid tumors and the acquisition of IFM Therapeutics which adds STING (stimulator of interferon genes) and NLRP3 agonist programs to its portfolio.

Regulatory news & approvals

Circassia Pharmaceuticals plc

Circassia Pharmaceuticals plc (Oxford, UK) (LSE: CIR) announced positive top line results for its respiratory drug Duaklir[®] in the treatment of chronic obstructive pulmonary disease (COPD) [4]. The results are from the Phase III AMPLIFY study being run by its partner, AstraZeneca. Duaklir is a fixed-dose combination of the long-acting muscarinic antagonist aclidinium bromide and long-acting beta-agonist formoterol fumarate, delivered using the PressAir dry powder inhaler, owned by AstraZeneca. AMPLIFY is a 24-week study which has involved around 1500 patients enrolled in Europe in which the performance of Duaklir is compared with that of each of the components of the combination administered as monotherapies. Top line results show that the study met both of its primary

end points; improvements in lung function, compared with the monotherapy comparators as measured by forced expiratory volume in 1 s.

Since the failure of its leading antiallergy treatments in late stage clinical studies, Circassia has been focusing on its respiratory products. From the deal with AstraZeneca signed earlier this year, it already has US rights to COPD drug, Tudorza (aclidinium bromide inhalation powder) and has several other treatments under development for asthma and COPD based on its propriety particle-engineering technologies. These include its version of leading drugs Seretide and Spiriva and Flovent/Flixotide.

Axovant sciences

Axovant Sciences (NY, USA) (NASDAQ: AXON) announced that its investigational drug Intepirdine (RVT-101) being developed to treat Alzheimer's disease (AD) has failed to meet its primary end points in a Phase III clinical trial [5].

It was hoped that the drug when used in conjunction with an already approved drug, donepezil (Aricept) would improve cognition. However in the study (which involved 1315 subjects aged between 50 and 80) no difference was measured between the Intepirdine and placebo arms in change from baseline in its two primary end points, cognition and activities of daily living after 24 weeks.

The intended mode of action of Intepirdine is as an antagonist of the serotonin receptor 6 (5-HT)₆, thus seeking to slow or reverse the impairment the serotonergic neurotransmitter system, which occurs as AD progresses.

This continues the losing streak in the development of new treatments for AD that has continued since 2003 (when the FDA last approved a new drug to treat this disease) and follows recent failures in drugs being developed by Eli Lilly and Co (Lilly; IN, USA), Lundbeck and Merck. Although the risks in developing drugs are high, it has been estimated that the costs of the disease in the USA are currently around \$260B per annum [6] creating a large market opportunity if effective treatments can be found.

More than 25 drugs are currently in Phase III and further eight in Phase II for the treatment of AD, which, if approved, could come to the market by 2025. Many of these compounds target pathways that are believed to be the cause of the disease, such as the build up of amyloid plaques or tau proteins and, unlike Intepirdine, seek to target the disease at a presymptomatic stage before significant cognitive impairment has taken place.

Axovant says they will work with investigators to conclude the MINDSET open-label extension study. Although this would appear to be the end of the road for Intepirdine in the treatment of AD, the company is running another study, HEADWAY, looking at Intepirdine in patients with dementia with Lewy bodies (DLB), which remains on track to report top line results at the end of 2017.

Eli Lilly

Lilly (NYSE: LLY) won approval from the FDA for Verzenio (abemaciclib), a CDK4/6 inhibitor to treat breast cancer [7]. CDK4 and CDK6 are cyclin-dependent kinases that regulate part of the cell cycle and are overactive in cancer cells. CDK4/6 inhibitor seem to be particularly effective in targeting estrogen receptor-positive breast cancer which seem to be highly dependent upon CDK4 for proliferation, but the mechanism of action should be applicable to other cancers. Lilly is also looking to use abemaciclib in combination with therapies for patients with metastatic breast cancer with an ongoing study, which is due to be completed in late 2019.

Pfizer and Novartis already have approved CDK4/6 inhibitors (Ibrance and Kisqali, respectively), so Verzenio will be entering a competitive market albeit one worth several billion dollars per annum. One of the side effects of Verzenio observed in the trials is a high rate of diarrhea, although Lilly argue that this is a manageable effect. Kisqali has a risk of mild cardiac arrhythmia, with ECG monitoring recommended to support its use.

Intarcia

Intarcia Therapeutics (MA, USA) received a complete response letter from FDA relating to its filing of ITCA 650, which is a novel drug device combination of exenatide for the treatment of diabetes [8]. The letter provides FDA's feedback on the application and the reasons that it will not be approved until deficiencies in the application have been addressed. The contents of the letter are confidential but Intarcia say they will work with FDA to overcome these and that no further pivotal clinical work is required.

Exenatide (a GLP-1 agonist) has been approved for several years for the treatment of diabetes and is currently delivered by injection. It is marketed by AstraZeneca as Byetta (for twice daily injection) and Bydureon as an extended release version (weekly injection). ITCA 650 utilizes Intarcia's Medici Drug Delivery System™ a

proprietary subcutaneous delivery system that combines formulation stabilization, and an implantable osmotic pump the size of a matchstick, which is implanted under the skin. The approach allows the controlled release of medications over periods of up to a year.

Intrarcia argues that this approach overcomes many of the medication adherence issues encountered by patients with Type 2 diabetes, who dislike injections or the side effects from oral medications.

Intrarcia has yet to give any estimation of how quickly FDA's concerns can be addressed although it has said they do not require any further pivotal clinical work.

The company has several other programs using its implant technology, including a collaboration with the Bill & Melinda Gates Foundation looking at the prophylactic delivery of anti-HIV therapy in areas where the disease is epidemic. So far the company has raised around \$600M in series EE finance.

Sandoz

Sandoz (Holzkirchen, Germany), a division of Novartis, announced that FDA has accepted its Biologics License Application for a biosimilar version of Roche's Rituxan[®] (rituximab) [9].

Rituxan is used to treat blood cancers including non-Hodgkin's lymphoma (follicular lymphoma and diffuse large B-cell lymphoma) and chronic lymphocytic leukemia, as well as immunological diseases such as rheumatoid arthritis.

To date there are seven biosimilars approved in the USA, but that number is set to further increase as more biologic patents expire over the coming years. Sandoz already has five biosimilars approved globally with another five anticipated to be approved by 2020, making it one of the leading biosimilar players in the market.

Sarepta Therapeutics

Sarepta Therapeutics (MA, USA) (NASDAQ:SRPT) announced positive top line results for golodirsen (SRP-4053), its next generation candidate for the treatment of Duchenne muscular dystrophy (DMD) [10]. The results from an on-going European study involving 25 participants, showed an increase in skipping exon 53 over baseline levels as well as an increase in dystrophin protein over baseline.

DMD is caused by a mutation in the gene for the protein dystrophin, which is important for the maintenance of the membranes of muscle fiber cells. This most commonly occurs genetically but can also be caused by new mutations. These mutations disrupt the production of proteins leading to muscle wastage and eventual death. Sarepta's approach to treating the disease is to utilize exon skipping in which a 'molecular patch' covers up the mutation and allows the protein encoding process to continue.

Its first drug EXONDYS 51TM (eteplirsen) injection was controversially approved by FDA in 2016 despite review panel of external experts who concluded that there was insufficient evidence to establish that the drug provided clinical benefit. FDA decided that there was reasonable evidence that the observed dystrophin production is reasonably likely to predict clinical benefit in some patients with DMD but has called for further clinical data to show clinical benefit in terms of improved motor function with an agreed final reporting date of May 2021.

Golodirsen works in a similar way but acts on exon 53 rather than exon 51. The 4053-101 study has been conducted in two parts, a randomized, placebo-controlled dose-titration phase followed by an open label extension in which all the study participants get the active drug. The published results are after 48 weeks of the open label extension at which point a biopsy from the biceps muscle was taken for the analysis. All 25 participants showed improvement in the end point measures. The significance in the results is that the increase in dystrophin levels was seen in the area of muscle (the sarcolemma) where it is required in order to have clinical effect. Although still quite low, the levels are higher than what were seen with EXONDYS 51.

The study is scheduled to continue for 144 weeks to evaluate safety and clinical end points.

ElectroCore

ElectroCore (NJ, USA) reported the first results at the 18th Congress of the International Headache Society from a study looking at noninvasive vagus nerve stimulation (nVNS) [11]. The multicenter, double-blind and randomized study, evaluated the efficacy, safety and tolerability of nVNS in 243 patients with episodic migraine treated with the company's GammaCore versus a control group who were given a sham treatment (placebo). GammaCore showed higher pain-free rates than the sham ($n = 123$) for the first treated migraine attack at 30 and 60 min as well as at 120 min after further *post hoc* testing. The device was well tolerated, as demonstrated by a low incidence of adverse effects.

GammaCore is CE-marked in the European Union for the acute and/or prophylactic treatment of primary headache (migraine, cluster headache and hemicrania continua) and medication overuse headache in adults). The device was also cleared in the USA in April 2017 for the acute treatment of pain associated with episodic cluster headache in adult patients. The company is also exploring a wider number of indications including epilepsy, depression, anxiety, gastroenterology and inflammation.

Nerve stimulation has been on the market for around 20 years since 1997, when Cyberonics received FDA approval for a surgically implanted vagus nerve stimulation for the treatment of refractory epilepsy. What is particularly appealing about the GammaCore technology is that it is noninvasive, requiring no surgical procedure to impact the device and electrodes.

Market news

Rani Therapeutics

Rani Therapeutics, (CA, USA) has raised, \$39M in Series D funding to accelerate the clinical development of its smart pill technology [12].

The company intends to use the funds to scale up manufacturing operations to support human clinical trials, which are planned to start in 2018.

The company is focused on the oral drug delivery of biologic drugs. Orally ingested biologic drugs tend to be metabolized by enzymes in the gut or in the liver before they can get into the systemic circulation. Attempts to develop formulation technology that can overcome this effect continue to be developed but have shown only limited success to date. Biologics drugs are currently generally administered using subcutaneous or intramuscular injection or by infusion. However, these approaches can be painful and/or time consuming and around 5–10% of the population are estimated to have needle phobia.

Rani's approach is to develop a smart pill that can travel through the gut and then anchor itself to deliver its drug payload through the intestinal wall.

Including this latest round, the company has raised around \$100M in funds so far, including from Google Ventures, other venture capital funds as well as from pharmaceutical companies Novartis and AstraZeneca.

Intracellular therapies

Intracellular Therapies has raised around \$150 million from a new public offering that will support its progress toward a filing with FDA for approval of its drug lumateperone to treat schizophrenia, which is anticipated in the next year [13].

Lumateperone is a dopamine receptor phosphoprotein modulator which selectively acts on dopamine D2 receptors, serotonin 5 which it is believed could enhance its effects on the negative symptoms of schizophrenia, such as social withdrawal.

The company is also looking to develop a long-acting formulation of lumateperone, which is due to start trials next year. Existing leading drugs for the treatment of schizophrenia (e.g., risperidone and aripiprazole) are already offered in long-acting forms by Janssen and Alkermes respectively, and these are considered to support improved long-term adherence, which is a challenging issue in schizophrenia.

The funds raised will also allow the company to progress other potential indications for the drug, including bipolar disorder and behavioral disturbances in dementia, which are in late-stage testing. It will also allow it to progress the development of PDE1-targeting compounds for the treatment of Parkinson's disease and other central nervous system disorders.

Patents & novel technology

Review article: use of microneedles in transdermal drug delivery

A review article was published that summarizes the current situation for the use of microneedles to deliver drugs transdermally [14]. A key challenge in transdermal delivery is the need to overcome the barrier presented by the outmost layer of skin, the stratum corneum. Microneedles penetrate through this region and have been shown to be effective in delivery medication into systematic circulation. However no products have yet been commercialized as other issues need to be addressed to show that this approach is safe and effective in drug delivery. Consideration of the degradation of the microneedle structure needs to be made; for example if fragments of the device break off they could cause irritation and potential immunogenicity. Although studies have shown that solid microneedles

can enhance the permeability of drugs for up to 5 h, there is a lack of data on how quickly the pores created by the device will close which could increase the risk of transfer of infection through the skin.

However, research published by a research team at Emory University, Atlanta, from a clinical trial looking at the use of dissolvable microneedle patches for influenza vaccination showed the approach was well tolerated and generated effective antibody responses [15]. About 70% of patch recipients said that they preferred this approach over other methods of delivery, so it is highly likely that the concerns mentioned above will be addressed and microneedle devices will be seen in the market in the next few years.

Allergan

In an attempt to maintain patent protection for its dry eye medication, Restasis and Allergan entered into a novel patent deal with the Saint Regis Mohawk Tribe [16]. The deal involves transferring intellectual property rights for the drug to the native american tribe and then being granted an exclusive license back of the rights. Allergan argues that the tribe holds sovereign immunity against a particular type of patent challenge at US Patent Trial and Appeal Board and so this deal can block challenges being made by several pharmaceutical companies including Teva and Mylan, who are seeking to develop and launch generic versions of the drug.

In 2002, Restasis was approved by FDA for the treatment of dry eye. The main patent on Restasis was due to expire in 2014. However, Allergan successfully applied for a new world patent that could extend the drug's monopoly until 2024. Shire won FDA approval in July 2016 for Xiidra, the first dry eye medication since Restasis. However, to date the drug has only gained a small share of the market compared with Restasis.

The Mohawk Tribe will receive \$13.75 million upfront and up to \$15 million annually as part of the deal.

Poor olfaction is a predictor of Parkinson's disease

Research published by a team led by Professor Honglei Chen from Department of Epidemiology and Biostatistics of Michigan State University suggests that a loss of smell can be a predictor of Parkinson's disease (PD) [17]. Professor Chen's work has focused using longitudinal cohorts to identify the environmental and genetic causes of PD with the aim of disease prevention and more effective clinical management. This latest research involved nearly 2500 participants (average age ~75 years) from the Health, Aging and Body Composition (Health ABC) study, a longitudinal study focused on risk factors for the decline of function in healthier older persons. The participants had their olfactory capability assessed using the Brief Smell Identification Test in 1999–2000. Subsequent monitoring for an average of 9.8 years identified a total of 42 subjects with PD up to 2012. Retrospective analysis for the olfactory capability assessment showed a correlation with risk of developing PD. Furthermore, the correlation was particularly strong for those diagnosed in the first 5 years of the follow-up with a higher risk from white rather than black participants.

These results are significant for the development of effective treatments or other preventive measures to address neurodegenerative diseases such as PD, which require early identification of subjects at risk prior to onset of disease symptoms (e.g., cognitive decline or movement disorders). The results point toward the potential of using low cost screening approach to identify high-risk populations who can then have further tests or start with preventative treatments.

Financial & competing interests disclosure

The author has no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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