SCRIP
CITELINE COMMERCIAL

26 Jun 2020 |

No Looking Back For Sanofi In R&D Turnaround Quest

Promise In Plentiful Supply, Data Less So

by Alex Shimmings

Sanofi's R&D operation has shaken the dust of diabetes off its feet with an update on its ambitious pipeline plans at an R&D day event.

Just six months since *Sanofi*'s new CEO Paul Hudson set out his vision for the company, he returned at a virtual R&D day armed with evidence of early progress in a bid to show investors that it is on the right track.

While he gave updates on the six programs already identified as priorities, the R&D day was mainly an exercise in emphasizing Sanofi's core therapeutic area strengths and highlighting its novel platform technologies, particularly the Nanobody multi-specific antibody technology (gained via its acquisition of *Ablynx NV*), and the Synthorin synthetic biology platform from *Synthorx Inc.*, which Hudson said are delivering novel, cutting-edge drug discovery capabilities.

"Our science is way better than people think," Hudson told analysts, admitting some convincing remained to be done on this score. "We know we are still a 'show-me' story," he said. Indeed, not that much in the way of new data were revealed during the day, analysts noted.

In December, at its capital markets day, and just three months into the job, Hudson announced his intention to take tough investment decisions, double down on a more focused pipeline, cut spending and restructure Sanofi's business units, including separating out consumer health care. His "roadmap"also included cost savings of €2.0bn ($2.2bn) by 2022, as part of which the company has subsequently confirmed it will lay off up to 1,680 jobs in Europe over three years, with a 1,000 expected to go in France. (Also see "*Sanofi Confirms Up To 1,680 Job Losses In Europe*" - Scrip, 29 Jun, 2020.)

SCRIP
CITELINE COMMERCIAL

This refined pipeline leaves no room for diabetes and cardiovascular disease R&D, the firm's historical forte, as it tilts from primary to specialist care.

Exiting cardiovascular and diabetes has been "a very heavy lift" for Sanofi, said R&D head John Reed. "It's a massive transformation of our organization," but it does free up resources to drive progress in specialty care, and the company is wasting no time on reflection here. As Hudson told journalists at a press briefing for the R&D day: "We're not looking back and doing too much analysis on how we used to be. We're looking forward."

Sanofi CEO Hudson Delivers An Ambitious Turnaround Agenda

By Jessica Merrill

10 Dec 2019 CEO Paul Hudson came to Sanofi's capital markets day with big news and key messages for investors about the company's future business model. *Read the full article here*

Indeed, the six priority programs outlined by the firm in December have had a rocket put under them, and some progress is already apparent. Quick wins have included the speedy start of the Phase III program for the brain-penetrating BTK inhibitor '168 for multiple sclerosis and first-in-human data for THOR-707, the "not-alpha" IL-2, one object of Sanofi's recent acquisition of Synthorx, and the prospective backbone of its immuno-oncology ambitions. (Also see "*Sanofi Bets Big On IO With Synthorx Buy*" - Scrip, 9 Dec, 2019.) On the market, expansion of the Dupixent (dupilumab) franchise has continued, with new approvals and indications, and it has been at the forefront of efforts to tackle the coronavirus, with two vaccine strategies in development. *(Also see "Sanofi Confident Of 'Tortoise And Hare' COVID-19 Vaccine Strategy*" - Scrip, 23 Jun, 2020.))

All six projects cover Sanofi's core competencies: immunology, inflammation, oncology, neurosciences and rare diseases, plus its vaccines expertise in infectious diseases (see below). And they are deemed by the company as potential first-in-class or best-in-class medicines, a descriptor that Sanofi claims could now be applied to 75% of its assets currently in development; it aims to increase this to 80%.

- Dupixent for atopic dermatitis, asthma, nasal polyps, eosinophilic esophagitis and COPD
- fitusiran & BIVV001 for hemophilia
- the oral selective estrogen receptor degrader '859 for breast cancer
- the BTKi '168 for multiple sclerosis
- venglustat for several monogenic disorders and for Parkinson's disease
- nirsevimab for respiratory syncytial virus

Reed said that when he arrived at the firm in 2018, 50% of the R&D budget was spent on primary care and developing "undifferentiated molecules for which it was difficult to make a real claim of best-in-class potential." Biosimilars too were "an enormous distraction from an innovation agenda," he said. "We had way too few first-in-class medicines in the pipeline. Our investments were also spread over eight therapeutic areas, with more than half of the R&D budget supporting primary care, as opposed to specialty care."

Reed added that it was no secret that only two of the last 12 medicines that Sanofi launched came from its own laboratories. The company intends to do better here too. 65% of its current candidates were originated in house – including oncology products the SERD '859 and the anti-CEACAM5 ('701) antibody drug conjugate – and it wants to increase this proportion to 70%. In this vein, it intends to explore gene therapy through an internal program, rather than by making an acquisition.

Efficiencies

Improving R&D efficiency through embedding digital and real-world data capabilities is another pillar of the new Sanofi, and Hudson credits this with the exceptional speed of '168 through the clinic so far. Its Phase I and II trials were conducted one year faster than the industry average, and COVID-19 notwithstanding, the first patient has now been enrolled into the Phase III trial program. "Four months after Phase II readout to have enrolled first patient says that we're serious, we're unencumbered, and we're ready to move quickly," said Hudson.

Sanofi's '168 is the second BTK inhibitor in development, noted analysts at SVBLeerink, and previously lagged *Merck KGaA*'s evobrutinib, on which Phase II data were published in June 2019. "Sanofi's announcement of the fast RRMS pivotal trial initiation and initial patient enrollment suggests '168 has passed Merck KgaA's evobrutinib in development," the analysts said.

Sanofi outlined an ambitious and broad development strategy for the product across the spectrum of multiple sclerosis, including relapsing-remitting, secondary progressive, and primary progressive disease.

Efforts to simplify how the R&D function works, by streamlining governance and giving teams more autonomy, have also borne fruit, Reed said. The company had been notoriously bureaucratic: "When I arrived at Sanofi, I discovered no less than 33 committees that made demands on the time of our clinical development teams. We cut that to three governance committees," he revealed. "It took 14 signatures and often several months for a portfolio of funding decisions to be processed so that a budget could be made available to the team to execute. Now, it takes less than 72 hours." Such changes, he noted, allowed the rapid start of the clinical trial of Kevzara (sarilumab) for COVID-19.

New Technologies To The Fore

Sanofi's novel technologies were at the fore. The limited new data that were released during the R&D day included biomarker data from the HAMMER study of THOR-707, a "not-alpha" variant of interleukin-2, in clinical development in multiple solid tumor types as both a single agent and in combination with immune checkpoint inhibitors.

The product uses the synthetic biology Synthorin platform, which expands the genetic alphabet through the creation of a new DNA base pair. Adding another new base pair to the two naturally occurring ones allows coding for a greater number of amino acids (up to 176 compared to 20 naturally occurring amino acids) and therefore a hugely increased diversity of proteins. This enables scientists build a new generation of precision medicines for oncology and autoimmune disease, Sanofi says.

Early biomarker data from a Phase I study of THOR-707 showed that the molecule increased tumor-fighting CD8+ T- and natural killer cells without significantly increasing regulatory T-cells and eosinophils, and reduced the risk of vascular leakage. Full Phase I results and the recommended Phase II dose are expected by 2021, and additional precision interleukins will be entering the clinic between 2021-2023.

"THOR-707 provides a perfect example of how we can use the Synthorx synthetic biology platform to develop highly innovative treatment approaches, in this case, boosting the impact of cancer immunotherapy," Reed said.

While not alone in this field (Roche also has a non-alpha IL-2 in development), Sanofi is among the leaders here.

SVBLeerink analysts said they were encouraged by 707's early data, and "are looking forward to seeing more complete data regarding the dose response, durability of effect, and whether biomarker findings translate to clinical efficacy."

Using the nanobody platform it obtained with Ablynx, Sanofi expects to have three to five new nanobodies entering the clinic each year in the near future. It also plans to enter clinical trials with bi- and trispecific antibodies targeting CD28 and CD38 for cancer immunotherapy, including the first trispecific T-cell engager, SAR442257, targeting CD38, a multiple myeloma antigen.

Pipeline Priorities

The first of the six pipeline priorities, and the company's main growth driver in the near-term, is the IL-4/IL-13 blocking pipeline-in-a-product Dupixent (dupilumab). First approved in the US In 2017 for atopic dermatitis, it has since gained expanded indications of asthma and nasal polyps and Sanofi remains confident it is a $10bn-plus asset. Further recent Phase III data show its potential in eosinophilic esophagitis and a decision has now been made to pursue COPD. Last

week, Dupixent received its first approval in China for atopic dermatitis. (Also see "*New China Approvals Include Amgen, Sanofi, Hengrui Drugs, Innovent Biosimilar*" - Pink Sheet, 21 Jun, 2020.)

Another potential "pipeline in a product" is the oral small molecule venglustat in development for several rare monogenetic diseases including Gaucher disease type 3, Fabry disease, and GM-2 gangliosidoses, but which Sanofi wants to expand to some more common indications.

Unlike the enzyme replacement therapies (ERTs), venglustat is a substrate reduction therapy (SRT) designed to reduce the accumulation of glycosphingolipids by inhibiting glycosylceramide synthase, a central regulator of glycosphingolipid metabolism. "The same biology has been implicated in some not so rare diseases with very high unmet need, for example, polycystic kidney disease and Parkinson's disease with GBA mutation," said Karin Knobe, therapeutic head for rare diseases and rare blood disorders development.

Sanofi hopes venglustat will become the first disease-modifying therapy for GBA Parkinson's disease; proof of concept data are expected by the first half of 2021. Pivotal results for autosomal dominant polycystic kidney disease are expected by Q4 2021, setting up possible regulatory filings from early 2022.

In rare disease indications, venglustat is in Phase II/III for Gaucher disease type 3, while a Phase III trial in Tay-Sachs disease (a type of GM-2 gangliosidoses) started at the beginning of the year and a Phase III Fabry disease trials is due to start next year. If all goes well, filings for all three indications could come in 2023.

Analysts at SVBLeerink pointed out that venglustat was an important defensive asset to offset increasing competitive erosion of legacy ERTs, and "potentially a major growth driver if venglustat works in multiple indications currently under investigation."

The two non-rare disease opportunities, they added, offered "significant upside to consensus estimates (~$500mm peak) because they add hundreds of thousands of addressable patients at rare disease premium pricing, but to date Sanofi lacks human data to demonstrate proof of concept in these indications."

The product will need to contend with competition from Idorsia's SRT lucerastat, for which pivotal data in Fabry disease are expected mid next year.

Tailored Hemophilia Franchise

In hemophilia, Sanofi wants to individualize therapy to suit patients' lifestyles with fitusiran and BIVV001.

While Roche's blockbuster Hemlibra (emicizumab) has had a transformative effect on the

hemophilia A market for patients with or without inhibitors, with its reduced frequency of dosing even up to four weeks, this comes with an efficacy tradeoff.

Fitusiran, an RNAi therapy, is being developed for patients with hemophilia A and B, with or without inhibitors, with once-monthly subcutaneous dosing and without the need for refrigeration.

Dietmar Berger said fitusiran had the potential to be the first true once-monthly subcutaneous injection with an annualized bleed rate of less than one, "raising the standard of efficacy for all hemophilia A patients." It is also on track to be the first subcutaneous therapy to address the hemophilia B population, which itself represents a $1bn market in the US alone, he added.

Phase II data for the product were released earlier this month, and Phase III trials are well underway. (Also see "*Promising Phase II Data For Sanofi's Hemlibra Rival Fitusiran*" - Scrip, 19 Jun, 2020.) A filing for adults and adolescents is planned in the second half of 2021.

BIVV001, being developed in collaboration with *Sobi AB*, is a potential new class of Factor VIII therapy for people with hemophilia A. The engineered Factor VIII product was acquired with Bioverativ, and is designed to extend protection from bleeds through high factor levels with once-weekly prophylactic dosing. A Phase III study in previously treated hemophilia A patients started last year and regulatory submissions could be made in the first half of 2022.

Sanofi believes the patient population is divided between those who want a near normal bleeding rate and those who prioritize convenience. It is pitching BIVV001 to be "the best option for those seeking an active life. With fitusiran, our target is to bring patient convenience and efficacy to the next level," said Vanessa Wolfeler, global franchise head of rare blood disorders.

Analysts at Bryan, Garnier & Co liked the plans: "The strategy to position the two drugs looks smart to us: BIVV001 for patients who have a very active life (lots of sport) thanks to its high efficacy, and fitusiran for those who want high efficacy with low injection burden."

The company is also pursuing a gene therapy program for hemophilia, though here it is well behind the frontrunners. However, it is using a lentiviral vector, against which patients are not expected to have pre-existing antibodies, while a sizeable percentage are expected to have antibodies to adenovirus vectors. It is expected to enter the clinic in 2022, by which time *BioMarin Pharmaceutical Inc.* and *Pfizer Inc.*/*Sangamo Therapeutics Inc.*'s products, SB-525 (giroctocogene fitelparvovec) and valrox (valoctocogene roxaparvovec), should be on the market.

The company has also decided to commit to establishing an AAV gene therapy platform within Sanofi from discovery to manufacturing, Reed said. "While we'll also tentatively explore other gene therapy approaches such as the lentivirus platform."

Reed added, “So within the next 12 to 18 months, we should be in a position to provide more specific updates on our progress with establishing the AAV platform in-house and in generating a compelling gene therapy pipeline.”