MEDTECH INSIGHT
CITELINE COMMERCIAL

12 Oct 2017 | **News**

Will AAA's Nuclear Med Offerings Turn M&A Buzz Into A Deal?

by Tina Tan

Advanced Accelerator Applications (AAA) has hit the headlines with recent rumors of a potential acquisition deal from Novartis. Now that the radiopharmaceutical company has its first therapeutic product approved and ready for commercialization, is AAA really ready to sign the dotted line?

With the recent European approval of *Lutathera*, the first theragnostic radiopharmaceutical of its kind to achieve this milestone, it is no surprise that *Advanced Accelerator Applications SA* (AAA) is looking more alluring than ever as an acquisition target for a pharma player.

Indeed, prior to the Oct. 2 approval announcement, AAA's name was already churning around the M&A rumor mill when media reports suggested that Swiss pharma giant *Novartis AG* was in talks with the French company over a potential acquisition. (Also see "*Will Radiopharmaceutical Company AAA Be M&A Fodder For Novartis?*" - Scrip, 28 Sep, 2017.).

When asked by *Medtech Insight* if there was any basis to these reports, AAA CEO Stefano Buono, commented that "in general," there has been interest from pharma. However, he added that there is also an expectation from drug companies to see if a radioactive drug, like Lutathera, would really take off in the market and become as successful as a conventional cancer therapeutic.

Radiopharmaceuticals has not had huge commercial success so far, according to Buono. The first radioactive drug by Baxter, *Zevalin* (ibritumomab tiuxetan), was approved by the US FDA in 2002 and even though it had demonstrated much better results than its comparator in clinical trials, it didn't have any commercial success, said the AAA CEO. "This scared the clinical community away from this idea of using a radioactive drug to treat a patient," he said. Then in 2013, a Norwegian company called Algeta with a prostate cancer drug Xofigo (radium-223 dichloride) was acquired by Bayer for $2.9bn, just as sales of Xofigo were getting started in the US and Europe. (Also see "*Algeta and Bayer agree $2.9bn sweetened takeover* " - Scrip, 19 Dec, 2013.) However, for all the high expectations pinned on this drug's market success, as reflected by the hefty merger

consideration, it also did not take off as well as expected and UK's NICE rejected Xofigo because there was not sufficient evidence of its cost-effectiveness for use in the NHS. (Also see "*NICE turns down Bayer's Xofigo*" - Scrip, 25 Mar, 2014.).

For a potential pharma buyer to make any advances beyond the discussion phase, Buono said AAA will need to prove that its radioactive drugs "will be a huge commercial success," which he strongly believes the company will do.

Buono's confidence in Lutathera succeeding whilst other similar drugs haven't lies partly in the simplicity of the platform on which the therapy is based. "We've made the platform very simple so that it is easy for the user."

Lutathera (lutetium (^{177}Lu) oxodotreotide) is approved for treating "unresectable or metastatic, progressive, well differentiated, somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs) in adults." It belongs to a class of drugs called peptide receptor radionuclide therapy (PRRT) in which octreotide – a peptide with a very high affinity with somatostatin receptors – is paired with a radioactive material, which, in the case of Lutathera, is lutetium (^{177}Lu). Lutathera is administered like conventional chemotherapy through an infusion drop into the bloodstream. Once in the blood stream, the molecule binds to the somatostatin receptor expressed on the surface of NET cells. The receptor brings the Lutathera molecule inside the tumor, where the radioactivity emitted by the drug kills the rumor cell from within, whilst having little effect on neighboring cells.

The European approval of Lutathera was based on results of a Phase 3 study, *NETTER-1*, involving patients with advanced midgut NETs. These patients were randomized to receive treatment either with Lutathera plus 30mg of octreotide LAR (long-acting repeatable) therapy or with a 60mg dose of octreotide LAR alone. The study met its primary end-point, showing that treatment with Lutathera resulted in a risk of progression or death that was 79% lower than the risk associated with high-dose octreotide LAR.

"We are using radiation that is well-known in radiotherapy of tumors, but so far used mainly for treating local tumors, not metastatic tumors," said Buono.

AAA on the rise

It is not just AAA's portfolio that would appeal to potential buyers. The company's statement income appears to back the commercial validity of the products it is selling. Its top-line has grown steadily year over year; from €69.9m in 2014 to €88.6m in 2015, and then to €109.3m in 2016. The upward trajectory has continued this year, with the French firm posting total revenues of €36.5m, above analysts' expectations of around €33.3m for the quarter. This represented a 32% sales increase in 2Q17 versus the same period a year

Lutathera enables this radiation to be delivered internally and in a targeted way so that it reaches metastasized cancer cells.

The approval of Lutathera means AAA can now offer a full theragnostic solution for NET patients; the company is already commercializing gallium-labelled somatostatin analogues for diagnostic PET imaging of NETs. NETSPOT (gallium ^{68}Ga dotatate) was approved by the US FDA in June 2016 and its European equivalent, SomaKit TOC, was approved by the European Commission in December 2016.

"This is characteristic of nuclear medicine to get two drugs from the same targeting molecule [for two applications]: one for diagnostics and the other for therapy. So we can couple the same targeting molecule with gallium or lutetium; we use NETSPOT/SomaKit TOC to first diagnose the tumor, then Lutathera if it is determined that the patient needs therapy," said Buono. The diagnostic can also be used later for monitoring the patient to see if there is a recurrence of cancer.

earlier.

European commercialization of Lutathera, together with the expected US FDA approval in early 2018, should bring short- to mid-term gains and bolster revenue even more.

Likewise, since it listed on the Nasdaq in November 2015, AAA's stock price has been on the up; it started trading at $18.50 on Nov. 9, 2015 and reached $58.30 on Sept. 26 this year, the day before the media report of the Novartis talks was released. This M&A speculation gave a further boost to AAA's stock value, and buoyed by the Lutathera approval, the company's shares now trade at the mid-$60 level.

The mid-sized pharma, founded in 2002 by Italian academics as a spin-off from the European Organization for Nuclear Research, has 21 production and R&D facilities that manufacture both diagnostic and therapeutic molecular nuclear medicine products, and over 530 employees in 13 countries (Belgium, Canada, France, Germany, Israel, Italy, the Netherlands, Poland, Portugal, Spain, Switzerland, UK and US).

AAA is planning to use this "simple but effective" technique of combining a single targeting molecule with radiation for diagnosing and treating other cancers. This includes prostate cancer, where AAA is currently investigating two candidates - 177Lu-PSMA-R2 and 68GA-PSMA-R2 – for treating, imaging and monitoring the disease. Again, lutetium is the radioactive isotope of choice for treatment and gallium for diagnostics; however, the targeting peptides will have a high-binding affinity for prostate-specific membrane antigen, a receptor on the surface of prostate cancer cells.

The firm's pipeline also includes using antagonist bombesin analogues, targeting gastrin-releasing peptide receptors, for diagnosing and treating gastrointestinal stromal tumors.

While the concept might seem simple enough, nuclear medicine is a far more complex business than conventional pharma companies would expect, warned Buono. " The logistics for the manufacture and supply of radiopharmaceuticals is very complicated and this is something that pharma companies, without experience of these products, cannot digest," he told *Medtech Insight*.

On the other hand, AAA already has over 15 years' experience of manufacturing and handling these types of drugs that have very particular properties, such as having only 10 hours of shelf life. "We deliver every day more than 1,000 doses to patients to over 200 patients, and that's the daily standard. We have this incredible know-how in daily manufacturing and delivery of the dose," he said. This expertise, Buono believes, will work to AAA's advantage of making Lutathera a commercial success – and potentially make the company even more attractive to industry suitors.

From the editors of Clinica