Pharmaceuticals & Biotechnology

Source: Eikon Thomson Reuters

Market data	
EPIC/TKR	**AGY**
Price (p)	14.0
12m High (p)	32.0
12m Low (p)	13.5
Shares (m)	636.2
Mkt Cap (£m)	89.1
EV (£m)	60.2
Free Float*	39%
Market	AIM

**As defined by AIM Rule 26*

Description

Allergy Therapeutics (AGY) provides information to professionals related to prevention, diagnosis and treatment of allergic conditions, with a special focus on allergy vaccination. The emphasis is on treating the underlying cause and not just the symptoms.

Company information

CEO	Manuel Llobet
CFO	Nick Wykeman
Chairman	Peter Jensen
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Key shareholders

Directors	0.7%
Abbott Labs	37.8%
Southern Fox	22.7%
Odey	6.9%
Blackrock	5.3%
Invesco	4.5%

Diary

1H'19	Ph.I Acarovac trial

Analysts

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ALLERGY THERAPEUTICS

Take an objective view

AGY is a long-established specialist in the prevention, diagnosis and treatment of allergies. The Pollinex Quattro (PQ) platform, an ultra-short-course subcutaneous allergy immunotherapy (AIT), continues to gain market share despite its availability in the EU on a 'named-patient' basis only. The aim of ongoing trials is to move the platform to full registration under the new regulatory framework. Positive outcomes in Phase III allergy trials are notoriously difficult to achieve because the primary endpoint is always subjective. Prudently, AGY included an objective secondary endpoint, which was highly significant, paving the way for regulatory discussion.

- **Strategy:** AGY is a fully-integrated pharmaceutical company focused on the treatment of allergies. There are three parts to its strategy: continued development of its European business via investment or opportunistic acquisitions; the US PQ opportunity; and further development of its pipeline.
- **Phase III PQ Birch trial:** The long-awaited results from the B301 Phase III Birch trial in 582 patients have been released. The study failed to reach its primary endpoint, which was based on subjective symptom scores, with no statistical difference between the active and placebo arms.
- **Objective endpoint:** Even though objective endpoints are not required for regulatory approval, AGY took the prudent decision to include one within the protocol of its B301 study. This demonstrated a highly statistically significant difference in immune response markers, IgG and IgG4, between the two arms.
- **Regulatory process:** Under the regulatory framework, there is a strong desire to have 'named-patient' products moved to full marketing approval. Even though the primary endpoint was not achieved, the strong objective endpoint indicating a sustained immune response could prove helpful in regulatory discussions.
- **Investment summary:** The market is likely to take a pessimistic view because of the failure to achieve the primary endpoint. However, regulators will not want to remove a product from the market that has resulted in improved clinical outcomes for thousands of allergy patients. Therefore, greater emphasis may be placed on the positive biomarker secondary endpoints, which are objective measures of immune response.

Financial summary and valuation

Year-end Jun (£m)	2016	2017	2018	2019E	2020E	2021E
Sales	48.5	64.1	68.3	74.0	80.0	88.0
R&D investment	-16.2	-9.3	-16.0	-16.0	-20.0	-15.0
Underlying EBIT	-12.3	-2.9	-6.4	-7.2	-9.0	-1.9
Reported EBIT	-12.5	-2.6	-7.4	-8.2	-10.0	-2.9
Underlying PBT	-12.5	-3.0	-6.5	-7.4	-9.3	-2.3
Statutory PBT	-12.2	-2.7	-7.5	-8.4	-10.3	-3.3
Underlying EPS (p)	-2.4	-0.5	-1.1	-1.1	-1.6	-0.5
Statutory EPS (p)	-2.3	-0.4	-1.3	-1.3	-1.6	-0.5
Net (debt)/cash	20.0	18.8	12.5	12.8	0.4	-30.5
Capital increase	11.0	0.0	0.0	10.4	0.3	0.3
P/E (x)	-5.9	-29.8	-12.7	-12.4	-8.9	-28.4
EV/sales (x)	1.2	0.9	0.9	0.8	0.7	0.7

Forecasts have not been revised following this trial result and may be subject to change
Source: Hardman & Co Life Sciences Research

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Phase III birch trial

Background

AGY has 10 allergy vaccines submitted to TAV for consideration…

…with the B301 trial aimed at moving PQ Birch to full marketing approval

In 2008, under the direction of the Paul Ehrlich Institute (PEI) and based on European legislation, the Therapieallergene-Verordnung (TAV, Therapy Allergy Ordinance) in Germany commenced a process to have allergy vaccines fully regulated. At the beginning of the process, documentation for 123 vaccines was submitted to the TAV for consideration, including 10 from AGY. By September 2018 (as announced at the PEI seminar), the number of products remaining in the process had been reduced to 58 (ca.47%) either through withdrawal of applications or being turned down by the PEI. All of AGY's products remain in the process to become fully regulated. The B301 Phase III Birch study was designed to support AGY's submission to the PEI to have PQ Birch moved from 'named-patient' to full marketing approval.

B301 PQ Birch trial

The B301 trial protocol was designed following positive outcomes in two Phase II trials…

Following positive results in two Phase II trials, which demonstrated a significant reduction in allergy symptom scores in patients treated with the vaccine, AGY embarked upon the Phase III B301 trial in a greatly expanded patient population.

…recruiting 582 patients across 59 centres in four countries

The B301 study evaluated the safety and efficacy of PQ Birch in 582 patients recruited across 59 centres in four European countries – Germany, Poland, Austria and Sweden. Following immunisation, patients were assessed for allergy rhinoconjunctivitis symptoms during the 2018 birch pollen season (May through July).

Importance of objective endpoints

Achieving Phase III primary endpoints in allergy trials is notoriously difficult…

…because they are based on subjective symptom scores

The ability to achieve positive primary endpoints in Phase III trials of allergy products is notoriously difficult. This is because the primary endpoint is subjective, with the patient assessing and scoring the severity of his/her symptoms. However, this assessment is prone to great variation, influenced by many factors such as how the patient has slept, what he/she has eaten, how much stress he/she is under, and the patient's general wellbeing (e.g colds, other allergies). Consequently, there is usually an apparent 'positive outcome' in patients in the placebo arm of the trial, making the ability to achieve statistical significance with the vaccine-treated group extremely difficult, as AGY has experienced in the B301 trial. At this point in time, we do not know whether there was an unusually high placebo response, or whether the vaccine-treated group failed to improve symptoms.

Hardman & Co has argued for some time that protocols should include an objective endpoint as well…

…even though it is not required for regulatory approval

Given the poor track record for such allergy trials, we have frequently asked companies operating in this field why they did not include an objective endpoint within the protocol of the study. The reasons are usually three-fold:

- it is not required by the regulators for approval;
- patients do not want to have blood taken unnecessarily; and
- this process adds to the cost and length of time needed to conduct the study.

Prudently, AGY did measure immunoglobulins…

…to provide a secondary biomarker endpoint of immune response…

However, given the high cost and length of time taken to perform these studies anyway, a small extension to either is not relevant and not a satisfactory explanation, especially when put into the context of the loss of value on publication of negative outcomes. Moreover, the regulators not requiring such data is not a rational argument for not generating it. Therefore, it was very reassuring to see that AGY took the decision to include the objective measurement of biomarkers of an immune response (immunoglobulins IgG and IgG4) as a secondary endpoint within the B301 protocol. This decision was wholly justified when, as seen in many other allergy vaccine trials, the primary, subjective, endpoint was not met.

…which highly differentiated the vaccine treated arm

The secondary, objective, assessment of immune biomarkers showed that there was a strong and sustained immune response in the active arm of the study ($p<0.0001$). It is not immediately obvious why the immune response on vaccination did not translate into a clear and measurable reduction in allergy symptoms in the treated patients. In our opinion, this finding will be the centre of future discussions with the PEI.

Regulatory outlook

Dilemma for the regulators

On the face of it, failure to reach the primary endpoint would lead to the withdrawal of 'named-patient' products from the market. However, we believe that the regulator will be reluctant to do this for three reasons:

- PQ Birch is the only ultra-short-course SCIT presently available, denying patients access to a product that has been used successfully for many years;
- the PEI will be well aware of the high placebo effect with subjective primary endpoints reported in many allergy vaccine trials; and
- in this specific trial, there are contrasting outcomes between the subjective primary endpoint and the highly significant objective secondary endpoints of immune response.

Consequently, once armed will the full analysis of the data, we believe that there will be an open dialogue between the PEI and AGY.

AGY is likely to make a subtle change to PQ Trees to protect sales

Finally, AGY has a range of similar tree allergen products based on the ultra-short-course PQ platform. We can expect a subtle shift in patients from PQ Birch to the very similar PQ Trees product, which is at no risk, currently, of being withdrawn from the TAV process.

Conclusion

These headline data will be viewed negatively by the market…

The initial reaction by the market to this news will inevitably be negative. This is understandable, because the results will add time and cost to the regulatory process and may even require a further, smaller, confirmatory trial. We believe, however, that this does also provide an investment opportunity for three reasons:

…but greater consideration of the objective endpoint of immune response may pave the way to important discussions with the PEI…

- First, when the market has time to digest the news and gives more consideration to the objective outcome of a clear immune response, it will realise that AGY has a strong case to put to the regulator regarding the effectiveness of the product.
- Secondly, if the PEI does force PQ Birch to be withdrawn from the market, we do not believe that a high proportion of sales will be at risk and think that these can be transferred subtly to other similar PQ products (e.g. PQ Trees).

…and help to generate a stronger protocol for the upcoming US Phase III trials

- Thirdly, it allows for further adjustments to be made to the protocols for the upcoming US trials, which increase the probability of success, pending the outcome of discussions with the FDA.

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