Evaluate Vantage

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Ipsen’s quick fix backfires

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A failed phase III trial has Ipsen clutching at straws to salvage its rare bone disease project palovarotene, which it bought for $1bn a mere 11 months ago.

“A largely derisked asset” was how Ipsen’s then chief executive, David Meek, described palovarotene at the time of the $1bn Clementia acquisition. Today it became abundantly clear that the rare bone disease project, which Clementia had brought with it, was nothing of the sort.

In December a safety concern prompted the FDA to halt dosing in children, and today Ispen said almost the entire palovarotene clinical programme was being paused after a futility analysis concluded that a phase III trial was heading towards failure. Not that this is Mr Meek’s problem any more as he departed in the wake of the regulatory hold last month, leaving what looks like a disastrous business development decision in his wake.

Ipsen shares dropped 22% today to more than a three-year low. The French company has now seen around half its market cap erased since the Clementia buy was announced last February, equivalent to a loss of around $5bn in valuation. An urgent need to refill its pipeline prompted the drugmaker to strike several deals in the past year or so, pursuing a strategy that has apparently left investors cold.

Doubts about palovarotene existed from the moment the Clementia deal was announced, as Ipsen seemed to be disregarding numerous red flags. These included an uncertain patent life for the project, diminished economics because of royalties payable to Roche, and the failure of a phase II trial back in 2018.

As such, Ipsen looks to have been undone by its haste to strike a deal here, and Clementia’s bankers apparently pitched the deal perfectly: a rare disease play with a quick route to market, a description that ticks the boxes for many deal-hunters at the moment.

Car crash

Palovarotene’s lead indication is fibrodysplasia ossificans progressiva (FOP), a very rare condition characterised by abnormal growth of bone in muscles and connective tissues, known as heterotopic ossification. Multiple osteochondromas, the development of multiple benign bone tumours, is also under investigation.

FDA approval could have come as soon as 2020, Ipsen executives claimed at the time, and forecast peak sales of $400m in FOP alone (*Ipsen takes a rare gamble on Clementia, February 25, 2019*).

The wheels started to come off in December when the FDA told the company to stop dosing children under the age of 14. Some palovarotene-treated patients had displayed early growth plate closure, which essentially

means that new bone stops being produced before a child is fully grown.

The implications of such an association for a therapy intended for chronic dosing, from childhood, are obviously dire. Today's news suggests that the phase III FOP trial was not going to work anyway, escalating the situation to a full car crash.

Ipsen apparently believes that not all is lost: "Signals of encouraging therapeutic activity were observed in preliminary post-hoc analyses," a press release claimed, and the independent data-monitoring committee recommended that the study be continued. It seems that trial design is being blamed, and the company will now scour the data for a way forward.

This is a flimsy basis for hope – even before considering the serious safety signal that remains unaddressed. Palovarotene has been written off by investors, and it seems likely that Ipsen will soon have to concur.

Palovarotene trial summary

Study	Enrolment	Status	Primary completion
Phase III safety & efficacy trial in FOP	90	Dosing stopped; suspended in paediatric subjects	Sep 2020
Phase II safety & efficacy trial in multiple osteochondromas	240	Suspended in paediatric subjects	Jan 2021
Open-label extension in FOP	58	Dosing stopped; suspended in paediatric subjects	Mar 2021
Open-label extension to prevent heterotopic ossification in FOP; France	17	Dosing stopped; suspended in paediatric subjects	Mar 2021
In-home evaluation of episodic administration in FOP	40	Suspended	Jun 2019
Earlier Roche study in emphysema	491	Completed	NA
Earlier phase II FOP study	40	Completed	NA

Source: clinicaltrials.gov & company announcements.