

Upcoming events - pivotal data for idasanutlin and an interim look at Proqr's exon-skipper



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Roche's Mirros study should prove idasanutlin's worth on top of chemotherapy, while Proqr hopes to Usher in a rare disease cure.

Welcome to your weekly roundup of approaching clinical readouts. Building on the success of Venclexta in acute myeloid leukaemia, Roche is turning its attention to idasanutlin, an antagonist of MDM2. First up are [pivotal data from the Mirros study](#) of idasanutlin on top of chemo in relapsed/refractory patients, and the key to success could be idasanutlin's use in combination with Venclexta.

Results from Mirros, a 440-patient trial, are expected in the current quarter, and if the study is successful Roche plans to file later this year.

Mirros is expected to show idasanutlin beating cytarabine alone in terms of overall survival. In a [phase I/Ib trial in heavily pretreated AML](#), idasanutlin plus cytarabine showed a [composite complete response \(cCR\) rate of 29% in all patients](#) and 42% in those given 300mg twice a day, the dose being tested in Mirros. The median duration of response was more than eight months.

There was [one dose-limiting toxicity of myelosuppression](#) with monotherapy, while diarrhoea, reported by more than 85% of patients, was dose-limiting in patients given 600mg twice daily.

Later, idasanutlin could improve on Venclexta. This BCL2 inhibitor, which is expected to lead the AML market by 2024, is approved first-line on top of chemo in older patients or those in whom induction chemotherapy cannot be used. By inhibiting MDM2 idasanutlin activates the tumour suppressor protein p53, which in turn promotes the degradation of MCL1, a known resistance factor to BCL2 inhibition.

In a [phase I/II study the combination of idasanutlin with Venclexta](#) showed a 46% ORR and 33% cCR rate in unfit relapsed/refractory AML. That study showed an improved safety profile over trials using higher doses.

Roche is also looking to first-line use with idasanutlin: a [trial in combination with cytarabine and daunorubicin](#) started last year.

Top AML products by 2024

| Product | Company | Mechanism | Annual indication sales (\$m) 2024e | Indication status | Setting/notes |
|----------------------|----------------------|---|-------------------------------------|-------------------|---------------------|
| Venclexta | Abbvie/Roche | BCL-2 inhibitor | 971 | Marketed | 1L |
| Xospata | Astellas Pharma | AXL inhibitor; FLT3 inhibitor | 545 | Marketed | FLT3mut, r/r |
| UCART123 | Cellectis | Anti-CD123 Car-T | 445 | Phase I | r/r |
| Tibsovo | Agios | IDH1 inhibitor | 358 | Marketed | IDH1mut, r/r |
| Vyxeos | Jazz | Topoisomerase II & thymidylate synthase inhibitor | 313 | Marketed | 1L, therapy-related |
| IDHIFA | Bristol-Myers Squibb | IDH2 inhibitor | 256 | Marketed | IDH2mut, r/r |
| Idasanutlin (RG7388) | Roche | MDM2 inhibitor | 242 | Phase III | r/r |

Source: EvaluatePharma

Exon-skipping

The rare genetic disorder Usher syndrome can be caused by a mutation in several genes. Patients have hearing loss caused by abnormalities of the inner ear and vision loss caused by retinitis pigmentosa, in which the light-sensing cells of the retina gradually deteriorate.

Proqr's exon-skipping oligonucleotide QR-421a (QRX-421), is designed to address Usher syndrome type 2, which is caused by mutations in exon 13 of the *USH2A* gene. Skipping should allow production of a shorter but still functional form of usherin, a protein crucial to the development of supportive tissue in the inner ear and retina.

QR-421a is in a [phase I/II trial, Stellar](#), and interim data should emerge by the end of next month.

The study has enrolled 18 subjects with mutant exon 13, who will receive a single intravitreal injection of QR-421a in whichever of their eyes has worse vision, with 50µg, 100µg and 200µg being evaluated. Six patients will be assigned to each cohort, with four receiving the exon-skipping and two given sham injection.

The study is focused on safety, but vision improvement measures are secondaries.

There is little in development specifically for this rare condition; [most of the trials highlighted](#) by the Usher Syndrome Coalition concern trials of retinitis pigmentosa therapeutics that might help alleviate some of Usher's symptoms.

Chances of success are hard to estimate, but analysts at Evercore ISI point to the "sustained efficacy" shown by ProQR's lead project, sepfarsen, in Leber's congenital amaurosis, another form of genetic blindness. It is suggested that this partially derisks ProQR's technology, and hence QR-421a, for which Evercore forecasts 2024 sales of \$433m. Judging by *EvaluatePharma's* consensus, the rest of the sellside is more circumspect.

QR-421a's annual sales (\$m)

| First launch | 2021e | 2022e | 2023e | 2024e |
|--------------|-------|-------|-------|-------|
| Dec 2021 | 2.4 | 12.1 | 22.2 | 55.9 |

Source: EvaluatePharma.