

SPECIALIST IN CNS DRUG DEVELOPMENT
INNOVATIVE TREATMENTS TO IMPROVE QUALITY OF LIFE

Full Year Results 2021 and Outlook 2022
Tuesday, March 15, 2022, 3:00 pm CET





FULL YEAR RESULTS 2021 AND OUTLOOK 2022 TELEPHONE CONFERENCE

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Speakers:

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Ravi Anand, CMO

Marco Caremi, Exec. VP BD

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Evenamide - schizophrenia

- TQT-Study 010 and EEG Study 008 both met their primary objectives: absence of arrhythmia risk in healthy volunteers, and of EEG/neurological abnormalities in patients with schizophrenia
- Newron initiated
 - open-label add-on study in patients with treatment resistant schizophrenia (TRS) and its extension (Studies 014, 015)
 - first randomized, placebo-controlled adequate, well-controlled, potentially pivotal study of evenamide in patients with chronic schizophrenia not responding adequately to second-generation antipsychotics (non TRS) (Study 008A)
- Strategic commercial/development partnering options being evaluated





Xadago®/safinamide – Parkinson's disease

- Partnership agreement with Zambon on potentially pivotal study in patients with levodopa-induced dyskinesia (PD LID)
- Newron, Zambon and Supernus acting to protect intellectual property rights in the US (Paragraph IV Notice Letters)

Corporate

- Fourth and fifth tranches of funding from EIB, of EUR 7.5 million, each; fully drawn, now (€40m)
- Newron continues to explore a number of potential pipeline opportunities to expand its pipeline in central nervous system diseases



COMPANY HIGHLIGHTS



Unique portfolio of innovative CNS product candidates

- Xadago® for Parkinson's disease – Global approvals validate Newron's development capabilities from research to market
- Evenamide – New concept in treating inadequate/non-response in schizophrenia
- Ongoing search for strategically relevant assets

Significant near-term value drivers for both candidates

Management team with extensive experience and proven track record in drug development and commercialization

Fully funded beyond key value inflection points

- Cash balance of € 34.6 million (December 31, 2021)
- Royalty income, R&D tax credit: approx. €16m (2 yrs.)
- Cash reach 2024



DEVELOPING UNIQUELY DIFFERENTIATED DRUGS FOR CNS TARGETS

Xadago® (safinamide)

Commercialized by partners in 16 European markets, the US, Canada and other markets for Parkinson's disease ("PD")



Newron receives milestone and royalty payments from sales of safinamide in PD; > € 65 million received to date

Evenamide (NW-3509)

Phase IIa trial demonstrated efficacy; potential first mechanistically validated treatment for poor/non-responding patients with schizophrenia



First pivotal study started Sept. 2021, as part of Phase III program in two indications. Opportunities for commercialization by Newron (TRS indication) and partnering (non-TRS indication)

INNOVATIVE CLINICAL PIPELINE WITH NEAR-TERM CATALYSTS

PRODUCTS		Phase I	Phase II	Phase III	Market	Commercial Rights
Xadago® (safinamide) ¹	 Adjunctive therapy in PD					Zambon
	 Adjunctive therapy in PD					Zambon/Supernus
	 Adjunctive therapy in PD					Meiji Seika/Eisai
	 Levodopa Induced Dyskinesia (PD LID)					Zambon/Supernus
Evenamide (NW-3509)¹	Adjunctive therapy in Schizophrenia					Newron
	Adjunctive therapy in TRS					
Ralfinamide¹	Orphan indication in neuropathic pain					Newron

Expected Milestones



Xadago®:

Preparations for study in patients with Levodopa Induced Dyskinesia (PD LID) ongoing, study expected to start Q3 2022



Ongoing search for strategically relevant assets



Evenamide:

- Safety and efficacy, six-week, randomized, double-blind, rater-blinded study in TRS patients (study 014) >150 patients, results expected in Q2/2022
- Minimally 200 pts phase II/III study started Sept. 6, 2021, results expected by QIV 2022, further pivotal study to initiate in 2022

¹ Safinamide, Evenamide and Ralfinamide all developed from Newron's ion-channel based research

**Xadago in PD
Marketed
compound with
opportunity for
second label**



- FIRST APPROVED NCE IN >10 YRS (US, EU)
- GLOBALLY LICENSED
- DOUBLE DIGIT/SINGLE DIGIT % ROYALTIES
>€65M MILESTONES/ROYALTIES COLLECTED
- TO REACH PEAK COMMERCIAL POTENTIAL,
GET SECOND LABEL FOR LID IN PD
 - 40% OF PD PATIENTS
 - ONLY 1 APPROVED DRUG (US, ONLY)
 - STUDY TO START IN 2022
 - ATTRACTIVE FINANCIAL TERMS



XADAGO®: NEW LABEL STUDY IN PATIENTS WITH LEVODOPA INDUCED DYSKINESIA

- Zambon previously discussed with the US Food and Drug Administration (FDA) the design of a potentially pivotal efficacy study to evaluate the effects of Xadago®/safinamide in patients with PD LID
 - Intention is to perform the study in the US, Europe and Asia/Australia
- Given Newron's experience in the development of Xadago, Newron to conduct the study
 - Zambon remains associated with the study
- Newron and Zambon to share study cost, equally, in return, Newron to qualify for a one-time milestone payment and a greater share of royalties should the study lead to a label extension
- Evidence indicating Xadago's anti-dyskinetic effect:
 - Mechanism, i.e. glutamate release inhibition
 - LID models in rats and monkeys
 - PD patient data: significant reduction of dyskinesia in 223 dyskinetic (Dyskinesia Rating Scale) PD patients in a 2-year, placebo-controlled study
- Agreement executed March 2021
- Preparations for study initiation ongoing
- Study expected to start Q3 2022

SIGNIFICANT COMMERCIAL OPPORTUNITY IN XADAGO® (SAFINAMIDE)

US / Canada	EU	Latin America	Israel	Japan / Asia	Australia / New Zealand
 Launched in US in 2017 Launched in Canada in 2019	 Launched in Germany, UK, Italy, Spain and other EU territories, Switzerland, UAE, Brazil and Colombia; application for regulatory approval filed for Mexico		 Approved in 2020	 Launched in 2019	 Launched in Australia in 2019

» Parkinson's disease affects 7 to 10 million people worldwide

» Long period of Xadago® market exclusivity (patent life: 2029 in EU, 2031 in the US); ANDAs filed QII/2021

» Milestone and royalty revenues to Newron since 2012



EVENAMIDE – THE COMMERCIAL OPPORTUNITY



Addresses medical need in key sub-populations, COM: 2033 (WW), 10 yrs exclusivity post approval (EU)

- First **add-on** antipsychotic to be approved for **inadequately responding** or **treatment resistant** patients
 - Up to **70%** of chronic schizophrenia population every (on average) 18 months (CATIE study), due to fading efficacy and side effects of current medication
 - Add-on therapy with **no dose-limiting side effects** a key advantage for patients and prescribers

>> **Partnering**
 - **First drug for treatment of TRS** since clozapine (1989)
 - >30% of schizophrenia population (with upside to 50%)
 - Premium pricing, easier HTA, fast penetration

>> **Partnering, yet:**

No new drug in development for TRS, thus evenamide would be an easy adoption; Newron could commercialize for this indication in some markets, as limited marketing resources required
 - **No antipsychotic has demonstrated benefit as add-on to clozapine, thus evenamide would be the only option** (Abt. 30k C-TRS patients in each key territory)
- >> **Newron's commercialization of C-TRS**

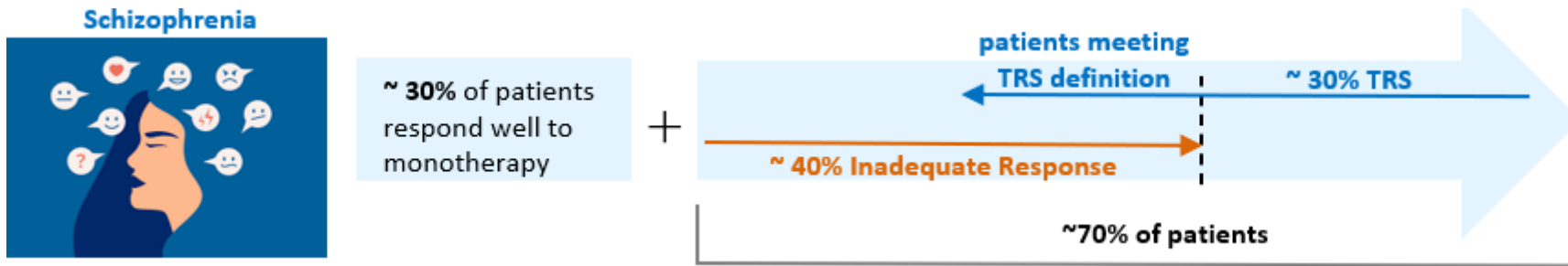
EVENAMIDE – TARGET PRODUCT PROFILE

Formulation: Oral

Dose: BID

Dual Indications:

- 1) **Add-on treatment Indication**...patients with **Inadequate Response** on their current antipsychotic monotherapy
- 2) **Add-on treatment Indication**...patients diagnosed as **TRS** (treatment resistant schizophrenia)
 - TRS is a **broad definition** that requires nonresponse to at least 2 sequential antipsychotic trials of sufficient dose, duration, and adherence



In **Clinical Practice** delineation between 1) **Inadequate Response Indication** and 2) **TRS Indication** becomes blurry; patient treatment management is similar, which includes; **raise** monotherapy dose, polypharmacy, **depot** inj., **switch** monotherapy



EVENAMIDE'S UNIQUE MOA DEMONSTRATED

Selectively blocks native sodium channels, showing no off-target effect on >130 CNS receptors, enzymes, transporters, etc.

Selectively blocks VGSCs in a voltage-and use-dependent manner

Modulates sustained repetitive firing without inducing impairment of the normal neuronal excitability

Inhibits Glutamate Release

Inhibition of native sodium channels expressed in rat cortical neurons

K_{rest} (μM)

25

K_{inact} (μM)

0.4

High frequency firing

Control

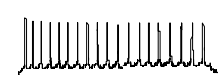


Evenamide 1 μM

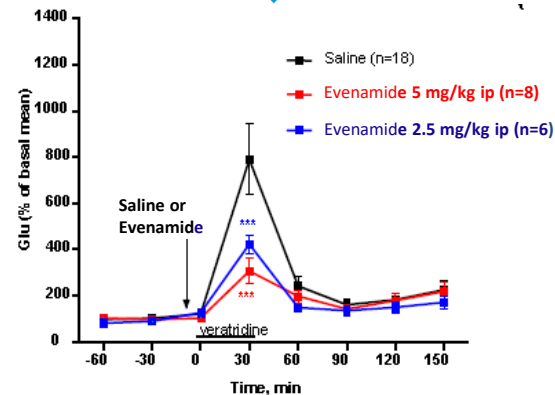


Low frequency firing

Control



Evenamide 1 μM



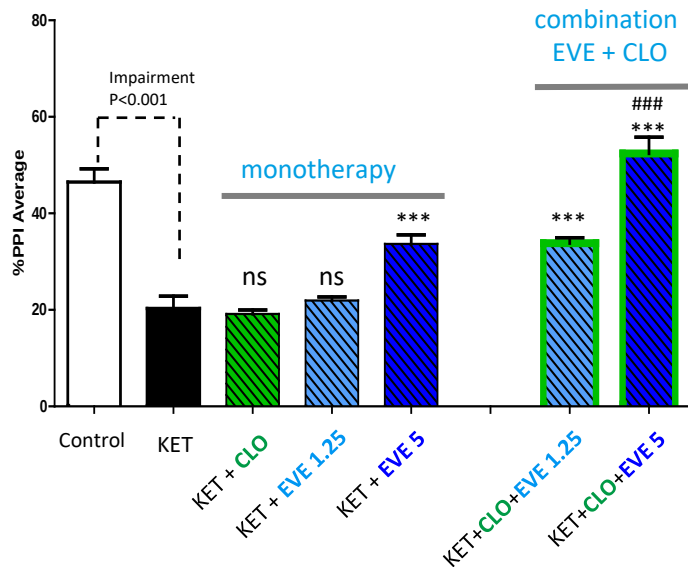
EVENAMIDE IS ACTIVE IN A WIDE RANGE OF SCHIZOPHRENIA AND PSYCHIATRIC ANIMAL MODELS AS A MONOTHERAPY AND AS AN ADD-ON TO EXISTING ANTIPSYCHOTICS

		Monotherapy	Add-on
Information Processing Deficit	Pre-pulse inhibition (PPI) disrupted by dopamine activation (amphetamine -rat)	✓	✓
	Pre-pulse inhibition (PPI) disrupted by NMDA antagonists (MK-801, PCP, -rat)	✓	
	Pre-pulse inhibition (PPI) disrupted by natural stimuli (sleep deprivation -rat)	✓	
	Pre-pulse inhibition spontaneous deficit (C57 mice)	✓*	✓
	Pre-pulse inhibition (PPI) disrupted by Ketamine in rat	✓	✓
Negative Symptoms	PCP-induced deficit in Social Interaction in the rat	✓	✓
Psychosis and Mania	Amphetamine induced hyperactivity in mice	✓	✓
	Amphetamine plus Chlordiazepoxide induced hyperactivity in mice	✓	✓
Cognitive Impairment	Novel object recognition in the rat: short term scopolamine impairment	✓	
	Novel object recognition in the rat: long term 24 hr natural forgetting	✓	
Impulse Control and Mood Symptoms	Resident–Intruder test in mice (Impulsivity)	✓	
	Tail suspension test in mice (Depression)	✓	
	Marble burying test in mice (Obsessive Compulsive Disorders)	✓	

*Trend
Blank cells = not evaluated



EVENAMIDE AS A MONOTHERAPY REVERSES THE PPI DEFICIT INDUCED BY GLUTAMATE DYSREGULATION DUE TO KETAMINE - COMBINATION OF INEFFECTIVE DOSES OF CLOZAPINE AND EVENAMIDE FULLY RESCUES PPI



Ketamine (KET) 10 mg/kg, SC, 45 min before testing
 Evenamide (EVE) 1.25 - 5 mg/kg, PO, 5 min before testing
 Clozapine (CLO) 3 mg/kg, IP, 30 min before testing

Statistics: 3-way, repeated-measure ANOVA; ***P<0.001 vs KET;
 ### P<0.001 vs EVE 5 (Tukey's post-hoc test) (n=16/group)

Minimal effective dose

Plasma concentration

Monotherapy: EVE 5mg/kg

76 ng/ml

**Add-on: in combination with
 inactive CLO 3mg/kg + EVE 1.25mg/kg**

19 ng/ml

**Full reversal produced by the combination of
 inactive CLO 3mg/kg + EVE 5mg/kg**

Studies performed by Dr Bortolato, Univ. Utah



EVENAMIDE: PROOF OF CONCEPT IN PATIENTS WITH SCHIZOPHRENIA DEMONSTRATED

- 4-week, placebo-controlled, add-on study of evenamide (15-25mg BID/day) in 89 patients on stable doses of aripiprazole or risperidone showing signs of worsening when compared to standard of care, at every assessment during the study (starting day 8)
 - **Significant improvement of**
 - PANSS positive, both mean change AND responder rate
 - CGI-C
 - **Superior benefit on**
 - PANSS total
 - LOF total
 - CGI-S
- Glutamatergic MoA seems to improve symptoms of psychosis in patients not responding to D2/5HT2 blockade



EVENAMIDE: REGULATORY INTERACTIONS

Health Authorities (Spain, Denmark, Sweden, Germany, UK, CHMP, US, Canada) in agreement with proposed Phase III plan

Newron provided additional informative studies as requested by the FDA prior to allowing Newron to initiate its Phase III development program

- Preclinical part of safety work has been successfully completed; no toxicity issues reported; submitted to FDA, already
 - First 4-week clinical safety (EEG) study completed in March 2021 (Study 008); 138 patients - no safety issues
 - Following recent discussions with FDA, Newron will address the remaining FDA issues once data from studies 014 and 008A studies are available
 - Safety and efficacy, six-week, randomized, double-blind rater-blinded study in TRS patients (study 014)
 - Outpatients suffering from TR schizophrenia, not responding adequately to an antipsychotic
 - >150 pts to be randomized, fixed doses of 7.5, 15, and 30 mg BID in 20 study centers in the EU and ASIA
 - Results available QIII/2022
-



EVENAMIDE: PHASE III CLINICAL DEVELOPMENT PLAN FOR SCHIZOPHRENIA INDICATION

Phase III program will cover specific populations:

- **Non-treatment resistant patients:** chronic schizophrenics experiencing inadequate benefit for symptoms of their psychosis, on current atypical antipsychotic monotherapy (risperidone, aripiprazole, paliperidone, olanzapine, or quetiapine)
- **Treatment resistant schizophrenia:** Patients whose psychotic symptoms are not responding adequately to any second-generation antipsychotic

First potentially pivotal Phase II/III safety and efficacy study 008A (**non-TRS**) in Europe, Asia and Latin America

- Four-week, randomized, 30mg bid versus placebo double-blind study to enroll > 200 patients ongoing
- Chronic moderate to severe schizophrenia patients on one of the leading 2nd generation anti-psychotics
- Start of study September 6, 2021, results expected by QIV 2022

Second potentially pivotal Phase II/III safety and efficacy study 003 (**TRS**)

- Eight-week, randomized, double-blind placebo-controlled Global study in >450 TRS patients
- Outpatients suffering from TRS being treated with one of the leading 2nd generation anti-psychotics
- Start of study by end 2022, results expected in early 2024

Option to add mania/mixed episodes indication for initial submission



NEWRON LISTING PROFILE AS OF DECEMBER 31, 2021

- Newron is listed at
 - SIX since December 2006 and
 - Since June 26, 2019, also at the Dusseldorf Stock Exchange (XETRA)
- Newron issues ordinary shares (nominal value 0.20€), only
- Number of outstanding shares as of Dec. 31, 2021: 17,845,345
 - Senior managers and Directors hold 100,140 shares (0.6%)
- Number of outstanding call options/derivative holding as of Dec. 31, 2021: 1,867,711/2,674,880
 - Senior managers and Directors hold 1,017,687 call options (5.7%)
 - EIB holds 807,169 warrant (4.5%)

Additional info can be found in Corporate Governance section of 2021 annual report: <https://www.newron.com/investors/reports-and-presentation/year/2021>





ANALYSTS AND MOST RECENT INFO ON SHAREHOLDINGS

Sell-side analyst coverage:

Jefferies Peter Welford

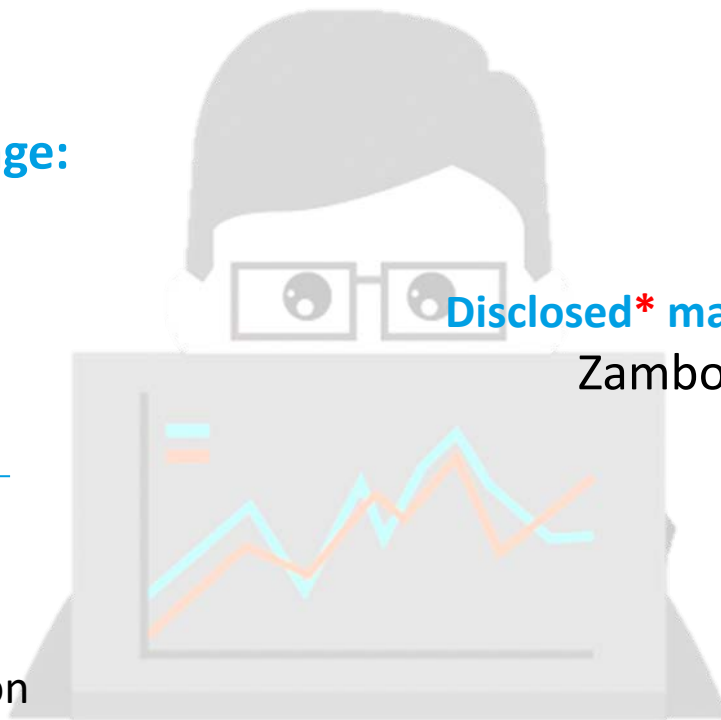
/ BAADER / Leonildo Delgado

Further coverage:

RX Securities, ValueLab, Edison

Disclosed* material shareholders (>3%)

Zambon > 4%



*: to the best of Newron' knowledge <https://www.six-exchange-regulation.com/en/home/publications/significant-shareholders.html?companyId=NEWRONPH>

Group Consolidated Financials (IFRS) FY 2021 – Income statement

EUR/000	2021	2020
Licence income	34	23
Royalties	5.728	5.235
Research and development expenses	(10.725)	(14.853)
Marketing and advertising expenses	(38)	(331)
General and administrative expenses	(7.356)	(8.140)
Operating loss	(12.357)	(18.066)
Net loss	(14.901)	(20.998)
Net loss per share - in EUR	(0,84)	(1,18)

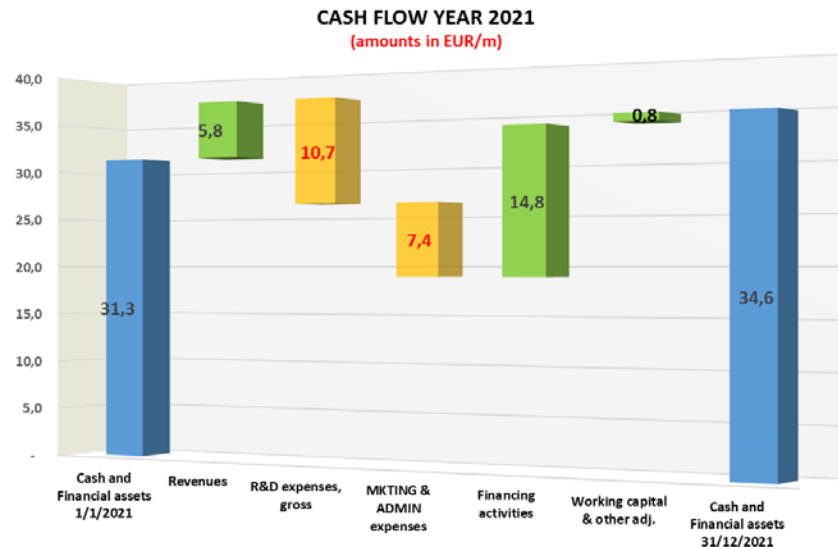


- Royalties increased by 9.5% (2020: 10%); substantial increase in USA (in 2020 Supernus Pharmaceuticals Inc. took over Xadago® from US WorldMeds) and launch in Brazil
- R&D expenses decreased following termination of all sarizotan related activities in 2020
- Delta between Operating and Net loss mainly related to EIB interests on 40m€ loan (2020 was 25m€)

Group Consolidated Financials (IFRS) FY 2021 – Balance sheet and Cash flow statements

EUR/000	2021	2020
Non-current assets	11.059	13.324
Current assets	4.833	6.624
Cash and other financial ass	34.594	31.250
Total shareholders' equity	3.107	17.246
Non-current liabilities	43.725	27.060
Current liabilities	3.654	6.892

- Non-current assets include 10.4m€ of R&D tax credit
- ✓ The amount Management expect to use in 2022 (2.1m€) has been reclassified in Current assets
- Cash and Other financial assets are sufficient to finance Newron' development activities into 2024
- Non-current liabilities includes: i) the EIB loan accounted for amortized cost; ii) the Lease liabilities and iii) the Employees severance indemnity



- Opening and year-end position, includes both Cash and Other current financial assets
- Financing activities reflects call of 15m€ from EIB
- Working capital includes: i) adjustments for non-monetary items; ii) accruals of EIB interests compensated by iii) decrease in Payables



AGENDA

1. Approval of the balance sheet as at 31 December 2021.
Connected and consequent resolutions
2. Redefinition of the number of the Board members.
Related and consequent resolutions
3. Appointment of the statutory auditors for the three fiscal-year time 2022-2024 and, therefore, until the approval of the balance sheet as at 31 December 2024, and determination of their fees. Connected and consequent resolutions
4. Appointment of the auditing company; connected and consequent resolutions





COMPANY HIGHLIGHTS



Unique portfolio of innovative CNS product candidates

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- Evenamide – New concept in treating inadequate/non-response in schizophrenia
- Ongoing search for strategically relevant assets

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Q&A



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