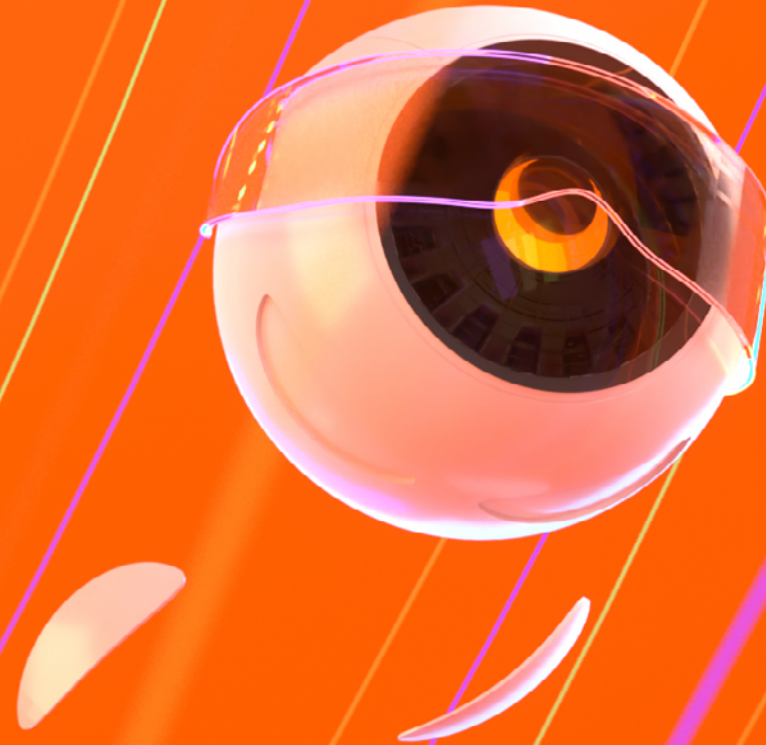


Investment Recipes

by  AtonRā Partners



10 FEBRUARY 2021

10 FEBRUARY 2021



AtonRâ Partners SA
www.atonra.ch

research@atonra.ch
+41 22 906 16 16

7, rue de la Croix d'Or
1204 Geneva | Switzerland

On the Menu

■ **Macro**
page • 3

■ **BIONICS**

A new era for ultrasound systems
page • 9

■ **BIOTECHNOLOGY**

Moving in on alzheimer's disease
page • 15

■ **SECURITY & SPACE**

**Cybercrime targeting the supply
chain**
page • 23

■ **SUSTAINABLE FUTURE**

Mobility SPACs attack
page • 28

CHARTS FOR THOUGHTS
page • 34

MACRO

A Glance Beyond The Headlights

Bubble talk is making headlines

Recent market behavior and the level of disconnect between fundamentals and some stock prices raised concerns by drawing similarities with the dot-com era.

- Inflation in scarce assets can be traced back to the Fed.
- But equities remain attractive as an asset class, at least in relative terms.

Unintended consequences are wide-ranging

Policymakers are caught into a trap of their own making. As they avoid the fall-out from downsizing the various programs put in place to support the global economy and the financial system, they end up stretching and dislocating the system.

- Unintended consequences at market, economic and social level are emerging.

What is really happening behind the scene?

A Hedge Funds' battle has taken place while media drove the focus on a group of retail investors. But the real winners were elsewhere to be found and the trading restrictions imposed by some retail brokers exposed the limitation of the entire financial system (e.g., T+2 settlement, clearing house, etc.)

- Well known and established Hedge Funds suffered massive losses and had to raise billions to stay afloat, while market-makers announced record profits.
- Technical elements are increasingly impacting the broader market, disconnecting it from its fundamentals.



Market Frenzy Evokes Bubble Memories

Similarities and differences with the dot-com era

The retail market frenzy, combined with record SPAC issuance and IPOs doubling on their market debut, lead investors to question the health of the equity market. These behaviors and patterns starkly remind of the dot-com era.

- Many financial metrics are indeed close to or above dot come era levels.
- However, negative real rates, easy fiscal and monetary policies, and a stated unwillingness by the Fed to raise rates are major differentiating factors.

Asset allocation: there is more expensive than equities

Fed policies created a much bigger bubble on the fixed income side. The 10y Bond P/E, which closely tracked the Equity forward P/E from the 70's up to the dot-com era, decorrelated and started trending upwards after the '08-'09 financial crisis (GFC) and even accelerated since the Covid-19 crisis.

- Forward earnings yields show a clear advantage for stocks vs. bonds.

Equity inflows

As written in our [2021 Outlook](#), there could still be a significant inflow into the equity market, driven by both institutional and retail investors.

- Major institutions might change their asset allocation models after revisiting the actual relative valuation as well as the risk-reward.
- Retail has not participated in the post-crisis rally of the past decade and, with the help of the various stimulus, might enter the stock market in force.

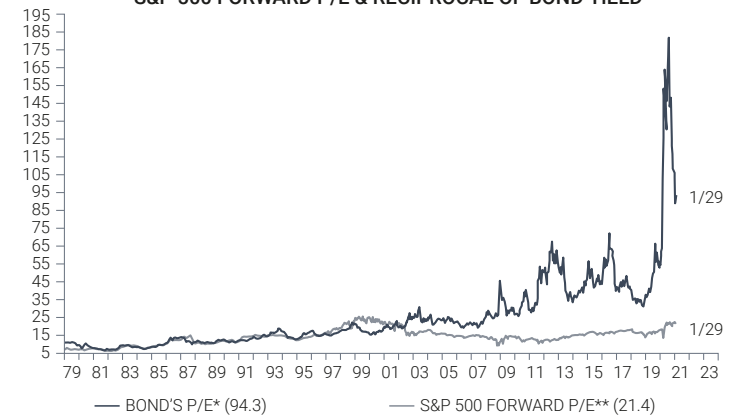
SOURCE:
AtonRā Partners

STOCKS VS. BONDS VALUATION MODEL
(USING 10-YEAR TREASURY BOND YIELD)*



* S&P 500 stock price index divided by S&P 500 fair-value price defined as S&P 500 12-month forward consensus expected earnings divided by 10-year U.S. Treasury bond yield converted to percentage. Monthly through April 1994, weekly after.

S&P 500 FORWARD P/E & RECIPROCAL OF BOND YIELD



* reciprocal of 10-year U.S. treasury bond yield.
** 52-week forward consensus expected S&P 500 operating earnings per share.
Monthly through march 1994, weekly thereafter.

Unintended Consequences

Market damage

The Fed managed to dampen the short-term effects of the 2008 financial crisis, but maintaining its various programs creates ever-larger market distortions, as it reduces the marginal benefit. Investors have been pushed further out along the risk curve to capture needed yield, while endless liquidity helps dilute the downside risk perception.

- The Fed zero interest rate policy has impacted most asset classes.

Economic damage

By inflating the bond bubble, the Fed (and policymakers) caused inflation for any scarce asset. An adverse consequence is the development of a “speculative” mentality, as people sheltered from downside risk expect to get rich via financial gambling and not from the production of goods and services.

- In the long run, relying only on imports of good and services would eventually weaken the entire economy and destroy the confidence in its currency.

Social damage

The Fed inflated financial assets expecting a wealth effect, but this did not materialize for the low and middle classes, which were not materially invested in equities. Increased inequality, the rise of populism, and movements like Occupy Wall Street 2.0 are just some of the expressions of this social damage.

- In 2016, the political establishment dismissed the impact of social media until they had to face Trump as newly elected president.
- In 2021, it is the financial establishment that may be doing a similar mistake.

SOURCE:
AtonRā Partners

Behind The Smoke Screen

A Hedge Fund battle

Media focused on Reddit-based traders, uniting to “fight” against Wall Street with its own weapons. But in our opinion, the real market-moving element was the eventual Hedge Fund (HF) battle, ignited in parts by the Reddit traders.

- The \$-volume of GameStop stock in January was \$130bn, meaning the 2m WallStreetBets subscribers had to trade ~\$60k each, seemingly implausible.
- A better explanation seems to be that Hedge Funds saw the squeeze opportunities and piled on it. Some already announced rich trading profits.

Market-makers the real winners

Market-makers thrive in a high-volume, high-volatility environment. With the large \$-volume and the wide bid-ask spread witnessed during the frenzy, they were given plenty of opportunities to make profits.

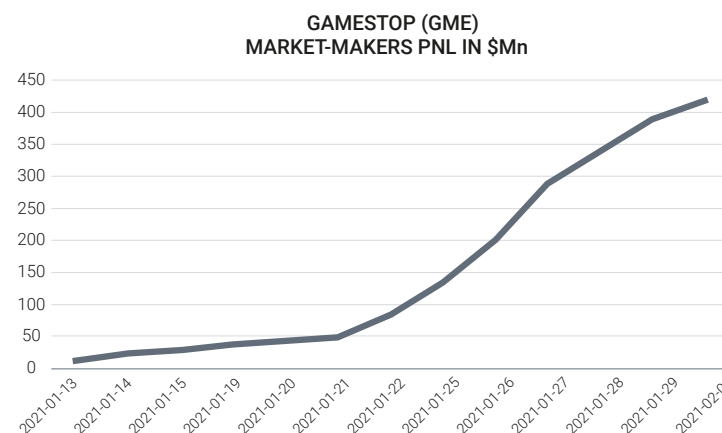
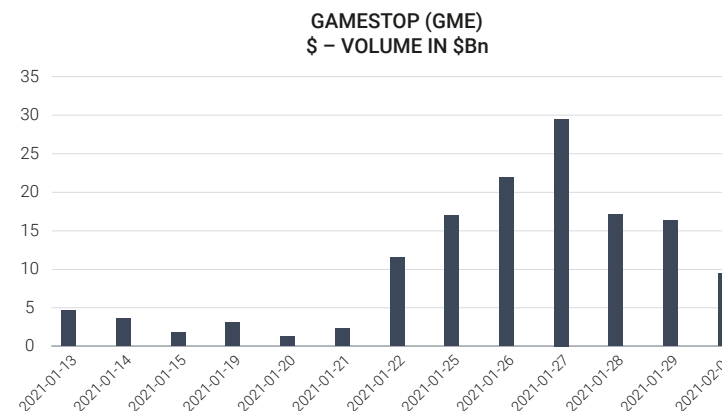
- Assuming 30bp bid-ask spread, they generated \$400mn just quoting GME stock.
- Market-makers’ P&L was also boosted by option trading, as pundits were ready to pay prices quoting ~1’000% of implied volatility.

Trading restrictions expose weaknesses in the system

The current financial plumbing settles on T+2. The clearinghouses, which process the trades, bear a credit risk and require collateral from the brokers. In turn, brokers restricted the purchase, but not the selling, of more than 50 stocks. For the retail punts, the game stopped.

- Brokers were asked billions of dollars of collateral to clear highly volatile trades.
- Fintech, blockchain and other new technologies can all contribute to improve a legacy system that is increasingly under stress.

SOURCE:
AtonRā Partners



Different Squeezes

The short squeeze

The short interest (SI) is the percentage of free-floating shares that have been sold short. When prices rise, short sellers must either meet the margin calls or buy back the shares. But these buybacks increase prices, requiring more buying, eventually squeezing the short sellers and forcing them to close their shorts at any price.

- GameStop SI has been above 50% since mid-2019 and reached above 100% in December 2020. In January, the stock rose by more than 2'500%.

The gamma squeeze

The short squeeze is linear. The gamma squeeze is exponential. Sellers of call options are de-facto holding a short position. To hedge their shorts, they must buy a delta-portion of the underlying shares, but, if the stock price increases, the required size of delta buying increases at an exponential pace (the gamma), accentuating the self-reinforcing reflexive effect.

- While the SI was significant, we believe the crash-up was mainly due to the gamma hedging. Market-makers, and probably some HFs, were short out-of-the money call options on GameStop (among others) and were forced to buy the underlying shares, in a self-reinforcing loop – a typical gamma squeeze.

The impact on the broader market

As market-maker and HFs are usually hedged, covering the shorts requires them to sell equivalent amounts of their long positions, which should have a neutral effect on the overall market. But the main indices were impacted only by the unwinding of the long positions, as the stocks being squeezed are not included in those indices.

- In aggregate, market participants have reduced their gross and net leverage.

SOURCE:

[Stock Market Briefing: Fed's Stock Valuation Model Monthly / Weekly](#)



Catalysts

- **Real negative rates.** It is in the interest of policymakers to keep real interest rates negative, even if inflation starts to rise. It is a natural incentive to deleverage the global economy, despite the side effects of uneven distribution of returns across asset classes and social groups.
- **Savings rates.** With Covid-19 related restrictions, household savings rates are at very high levels, and likely to be funnelled into the financial markets, for lack of alternative investment opportunities.
- **Equity under allocation.** Institutions, from CTA (because of high vol) to pension fund (because of valuation and models), are mostly under allocated in equities and likely to adjust over time.

Risks

- **Option gamma.** The market structure is shifting with the volume of options surpassing the volume of stocks. Derivatives are becoming the driver of stocks.
- **RobinHood effect on volatility.** Market distortions when a lot of retail flow will come to gamble might lead to systemic risks. While the linear market absorbed the flows without significant damages, massive retail flow on volatile products can have devastating effects.
- **Financial plumbing.** To absorb high volume and high volatility, the financial plumbing needs to update to a new reality. The systemic risks are growing.

Bottom Line

- An army of small traders squeezed short sellers on defunct companies causing their prices to skyrocket beyond imagination. The retail flows should not be underestimated and can come in force following the stock market performance of the past decade and the stimulus checks. Fed actions limited the short-term damages post-GFC but resulted in relative bubbles across asset classes. Unfortunately, they did not translate into the expected wealth effect across the population, rather increasing inequality and the disconnection between main street and wall street.
- The new investing tools for the retails are showing the limits of current market plumbing at times of stress. Fintech, blockchain and other new technologies can all contribute to improve a legacy system that desperately need to be upgraded.

Companies mentioned in this article:

GameStop (GME US), Reddit (not listed)

A NEW ERA FOR ULTRASOUND SYSTEMS

A Window Into The Human Body

A niche market poised for growth

Traditional ultrasound usage has been constrained by high upfront system costs and limited mobility. New hand-held ultrasound systems offer a cheaper, and easier alternative, opening the door to expand beyond traditional settings.

- Traditional systems cost \$30k–\$200k, vs. <\$20k for portable devices.
- The global market for portable ultrasound machines is poised to show a 13% 5Y CAGR, reaching \$1.6bn by 2025.

AI, AR, and semiconductors are renewing portable ultrasounds

Portable ultrasounds were introduced around 40 years ago. However, the technology has changed little until new semiconductor technology coupled with the introduction of AI and AR, helped unlock the full potential of this market.

- The global ultrasound industry has been dominated by the likes of Philips, GE Healthcare, and Siemens Healthineers.
- Disruptive innovation is coming from small new companies.

A new challenger defying the giants

Butterfly, a new market entrant, is making quick in-roads in a stuffy market by offering a high-quality, affordable, and easy to use portable ultrasound system.

- Butterfly's iQ+ system costs around 3k, compared to 5k–20k for portable devices with similar performances.
- The iQ+ system provides whole-body imaging with only one probe.

SOURCE:

[Global Portable Ultrasound Equipment Market 2021 By Manufacturers, Regions, Type, Global Industry Future Trends, Growth Key Factors, Demand, Business, Sales & Income, Application, Scope, Forecast To 2025](#)



Democratizing Ultrasound Imaging

A game-changing technology at the early innings

The medical community relied for years on bulky systems, which started to be replaced by lighter, cart-based or compact systems. Handheld ultrasounds, offering higher portability at a lower cost, have been introduced only recently.

- The global Point-Of-Care Ultrasounds (POCUS) market (which includes cart, compact and handheld devices) is estimated to be ~\$6bn, of which handheld ultrasound systems account for less than 3%.

Filling a need, especially in under-served areas

Ultrasounds are the most widely used diagnostic imaging modality, and portable systems are making it more accessible and affordable, especially in developing countries and rural areas.

- Currently, around 4.7bn people lack life-saving access to medical imaging.
- ~70% of medical technology is designed and used only in developed countries.
- Portable ultrasounds may help reduce maternal and infant mortality rates, as well as diagnose HIV, tuberculosis, and pneumonia.

Beyond traditional settings

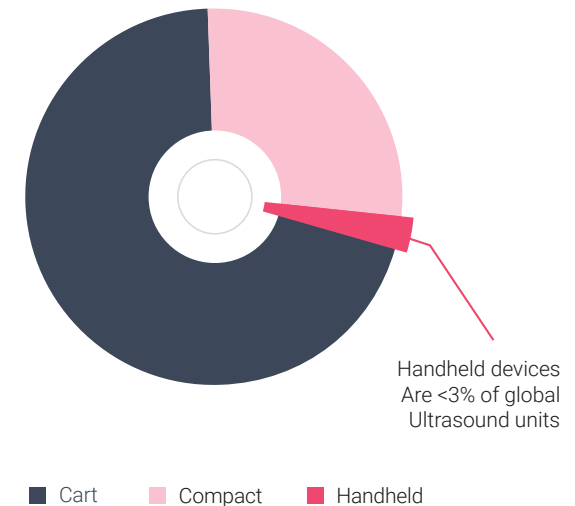
As the quality of the technology continues to improve, portable systems will extend to new clinical settings and support the diagnosis of a larger set of medical problems.

- Portable ultrasound systems are being used in cardiology, gynecology, obstetrics, radiology, urology, anesthesiology, and much more.
- Hand-held systems may expand beyond hospitals and imaging centers, entering practitioners' private offices, emergency rooms, ambulances, and even homes.

SOURCE:

[Barriers for medical devices for the developing world, Butterfly Investor Presentation 20,11,2020](#)

~\$6BN POCUS MARKET
ULTRASOUND BREAKDOWN



Sources:

1. GE Healthcare Investor Presentations
2. IHI Market

A Niche To Be Conquered

The devices market is crowded by big names

For both classical imaging devices and POCUS, the market is mostly owned by big names such as GE Healthcare, Siemens Healthineers, and Philips, all serving mainly hospitals and clinics in developed countries. But the trend is toward more portable and flexible solutions.

- POCUS have been out-selling traditional bulky devices over the last few years, being bought by hospitals and clinics.

The hand-held market is led by small players

Innovators in the hand-held ultrasound device market are small companies, able to compete on price with traditional systems, and looking to exploit the cost advantage to access underserved emerging markets.

- >80% of players are less than 20 years old and small or mid-sized.
- On average handheld solutions cost 2%–5% of a traditional cart-device (\$100k).

Lower reimbursements favor cost-leaders

Diagnostic imaging is also driven by reimbursement policies. The current trend to lower reimbursements is likely to favor cost-efficient private imaging centers, investing in cheaper devices.

- Inflation-adjusted Medicare reimbursement for all imaging modalities decreased between 2007 and 2019 by 40% on average.
- Ongoing transition of imaging services back to practitioner's private offices represents an appealing opportunity for cost-effective imaging systems.

SOURCE:
Journal of the American College of Radiology,
GRANDVIEWRESEARCH

KEY PLAYERS

FUJIFILM
Value from Innovation

SONOSITE

ALPION
MEDICAL SYSTEMS

 GE Healthcare

PHILIPS
Healthcare

Boston
Scientific

HITACHI

 **FUKUDA**
DENSO


Benq
Medical


Cephasonics
Ultrasound

CHISON
Value Beyond Imaging

 clarius

Canon
CANON MEDICAL

Next-Generation Portable Ultrasounds

Traditional devices: piezoelectric-based ultrasound systems

Traditional ultrasound systems rely on piezoelectric micromachined ultrasonic transducers (PMUT). Crystals vibrate and produce ultrasound waves when an electric current is applied. The waves that bounce back from the human tissues are recorded by a probe as an electric signal and turned into images.

- Several probes are needed to obtain imaging at different tissue depths.
- Labor-intensive assembly of individual, probe-specific, fine-tuned crystals, designed to produce the right type of ultrasonic wave, is expensive.

Next-generation devices: capacitive-based ultrasound systems

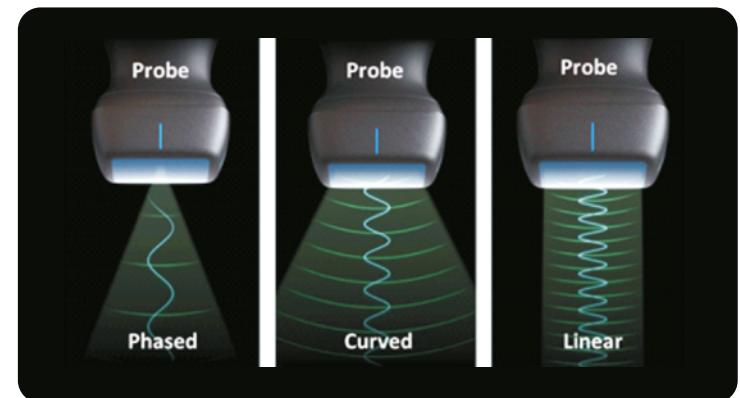
An emerging technology, called ultrasound-on-chip, replaces the PMUT with a single silicon chip containing an array of ~9000 micromachined ultrasound transducers (CMUTs), acting like a small drum vibrating when a voltage is applied. CMUTs are integrated with electronic circuits on a single chip.

- CMUTs 2D phased arrays can be programmed to produce and detect several ultrasonic waves, so a single probe can be used for whole-body imaging.
- The technology leverages large-scale semiconductor manufacturing processes (e.g., Butterfly uses the world's first 12" MEMS wafers produced by TSMC).

Powered by AI and AR

When combined with deep-learning models and AR, portable ultrasounds can support diagnostic decisions, be more user-friendly, and require less training.

- AI may provide automated measurements and anomaly detection.
- AI and AR may help the user to position the probe in the right place to maximize the image quality.



SOURCE:

Butterfly Networks, Yole,

[CMUT/CMOS-based Butterfly iQ - A Portable Personal Sonoscope](#) (Joyce Y Liu, BA^a, Jiajun Xu, MD^b, Flemming Forsberg, PhD^c, Ji-Bin Liu, MD, FAIUM^c)

Butterfly Network: A Promising Contender

The one ultrasound device for all

The iQ+, Butterfly's main product, is the first hand-held universal ultrasound device capable of imaging an entire body. Its versatility and portability make it suitable for all medical specialties.

- Butterfly embarks CMUTs in iQ+, resulting in a single-probe, light-weight, connected device.
- Connected to a smart-phone and backed by cloud-based smart tools.

An innovative business model

With its device, Butterfly Network is offering a Software-as-a-Service platform, where the client is billed monthly to get access to several services such as telemedicine, insurance billing, Electronic Health Record (EHR) integration, unlimited images storage, and sharing, etc.

- The service is tiered for different users enabling up-selling opportunities.
- Imaging services is a market currently estimated at ~\$2bn.

Targeted at the "average doctor"

The company is targeting the general medical profession, providing a packaged offer that includes an easy-to-use device enhanced by AI tools, as well as additional services accessible through the cloud.

- Customers can buy Butterfly iQ+ system (and get access to the cloud-based tools) with a one-time payment of ~\$3k.

SOURCE:
Butterfly,
Bloomberg



Catalysts

- **Lower reimbursement rates.** Low reimbursement policies drive the need for cost-effective devices in private diagnostic imaging centers.
- **Affordability.** Improved technology and a lower price tag open the door to access underserved emerging markets.
- **AI-based diagnostic services.** Faster and more reliable diagnostics, thanks to the use of AI-based tools, help increase usage for POCUS systems also outside of hospital or clinic settings.

Risks

- **M&A activity.** The market is only relatively fragmented, and the established big players could scoop-up investment opportunities before they go public.
- **IT limitation.** The use of portable ultrasound for diagnostic requires an adequately safe IT infrastructure to handle patient data in compliance with regulatory and insurance requirements.
- **Lack of training.** For non-imaging specialists, a lack of training lowers the usability of ultrasound devices for better diagnostics.

Bottom Line

- Ultrasound imaging is a reliable diagnostic imaging technique. The democratization of ultrasound imaging could reduce the lack of access to a proper medical diagnostic for ~5bn people, as the price and medical training barriers are being lifted by the commercialization of cost-effective portable ultrasound devices paired with AI-based diagnostic tools.
- We have built exposure in our Bionics portfolios to this niche, fast-growing market and keep scouting for more opportunities.

Companies mentioned in this article:

Butterfly Network (not listed), GE Healthcare (GE US), Philips (PHG US), Siemens Healthineers (SMMNY US), TSMC (2330 TT)

MOVING IN ON ALZHEIMER'S DISEASE

An Urgent Need For New Solutions

A complex, multidimensional health condition

Alzheimer's disease (AD) is an irreversible neurodegenerative condition affecting ~50mn people worldwide and the main cause of dementia, with no effective treatment on the market so far.

- AD is a significant public health concern; the associated economic burden is estimated ~\$1tn worldwide and is expected to drastically increase over time.
- The hallmarks of AD are progressive memory loss and cognitive dysfunctions, but secondary effects such as psychosis make the unmet need multidimensional.

A broad research effort

Despite decades of intensive research, there are still no effective treatments that can slow down or halt the progression of the disease. However, several intervention modalities are gaining traction.

- The quest for effective treatments is an industry-wide effort that includes neuromodulation devices, biological drugs, and small molecules.
- The disease's progression makes prevention and early detection the holy grail for the industry, with vaccines and early-stage diagnostics as key elements.

Innovation is the key to a solution

Promising drug therapies and technologies on the horizon bring a wave of cautious optimism to the fight against AD.

- Biogen is waiting for aducanumab's approval from FDA in the coming months, which would be the first new drug to reach the market in almost two decades.
- Athira, an emerging player in the field, is bringing a novel approach to treat the disease and showed promising results in a Phase 1 study.



A Public Health Concern

A neurodegenerative condition

AD is assumed to be caused by proteins aggregates in the brain interfering with cell-to-cell communication and leading to a progressive decline of memory.

- The main neuropathological hallmarks of AD include the accumulation of beta-amyloid ($A\beta$) plaques in the extracellular space of the brain and abnormal deposits of Tau proteins inside neurons, inducing cell death.
- The progressive death of neurons leads to dementia, the 5th leading cause of death in the U.S. among the >65 years old.

A high rate of failures in clinical trials

Failure rate during drug development is extremely high, with 99% of clinical trials failing to meet pre-specified endpoints. Hypotheses claim that patients' symptoms in clinical trials are already too advanced to be treated.

- No drug has been approved by FDA for the treatment of AD since 2003, but new promising technologies and drug pipelines are on the horizon.
- The treatment of patients as early as possible, and standardization of tests using accurate biomarkers would likely lead to increased drug approvals.

A large market opportunity

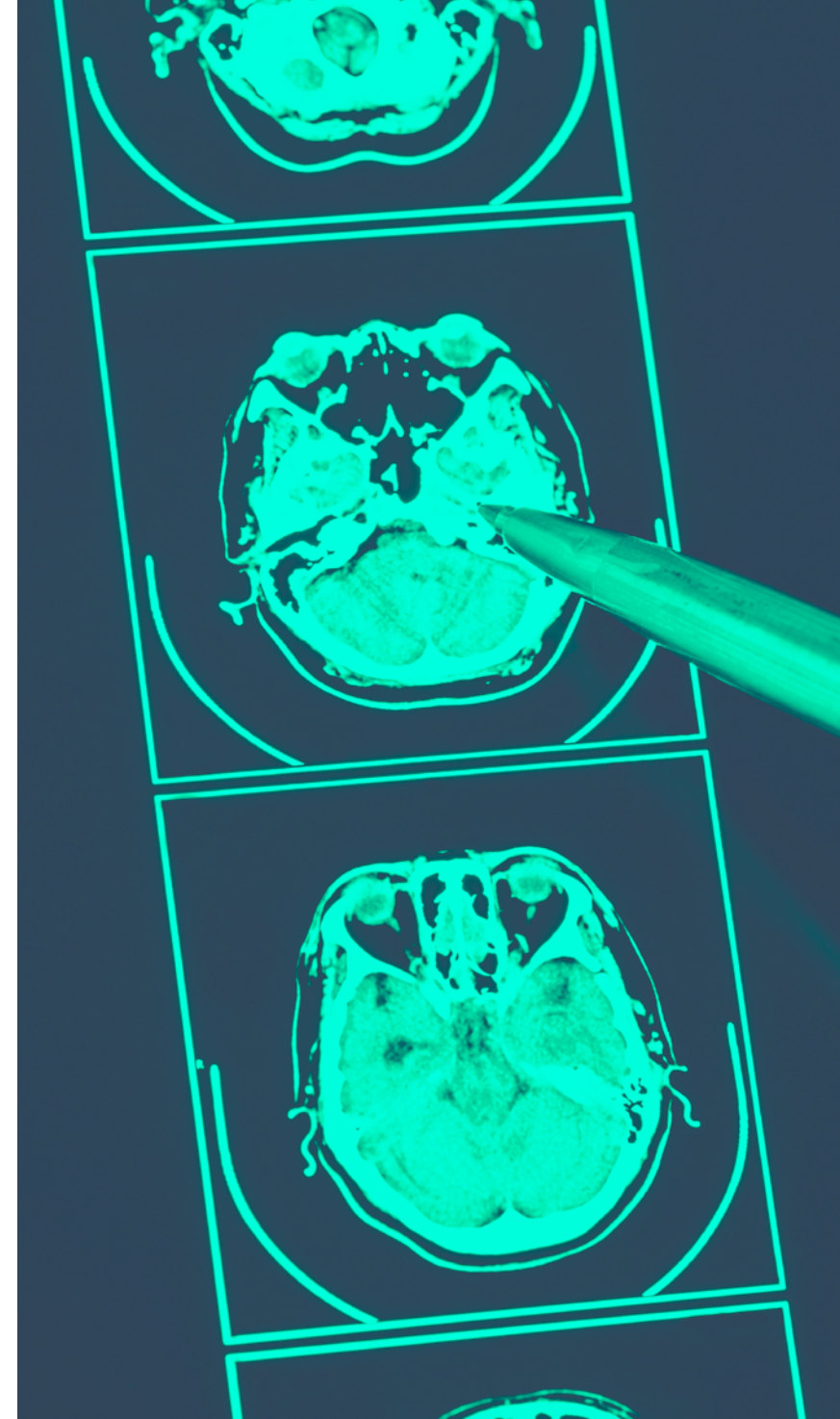
The increasing prevalence of AD due to aging population and emerging drugs and techniques to diagnose or fight the disease, lead to sizeable market opportunities.

- AD is affecting 5mn people in the U.S. alone with an associated economic burden of ~200bn and expected to double by 2050.
- The AD market is predicted to reach \$13.6bn by 2027 with a 9.23% CAGR. We believe that if new drugs are approved, these numbers will significantly increase.

SOURCE:

[Current and Future Treatments in Alzheimer Disease: An Update.](#)

[Alzheimer's Therapeutics Market to Reach USD 13.57 Billion By 2027 | Size, Share, Industry Analysis and Global Forecast to 2027](#)



A Multidimensional Battle

The relation between Alzheimer's, dementia, and psychosis

Alzheimer's is a leading cause for dementia, and 30% of dementia patients experience psychosis as part of their disease, often posing a greater challenge to patients and caregivers than the actual cognitive decline.

- The psychotic effects, which include hallucinations, delusions, and agitation, are considered to be the result of patients trying to resist their cognitive decline.
- Dementia patients with psychosis are also twice more costly to treat due to an increased need for nursing home placement and hospitalizations.

Plenty of room for improvement

There is currently no approved treatment for Dementia Related Psychosis (DRP), and the standard of care is inherently suboptimal.

- Elderly psychosis patients are currently being treated off-label* with atypical antipsychotics, a class of mood disorders drugs that carries a specific black-box warning** for increased mortality with elderly dementia patients.

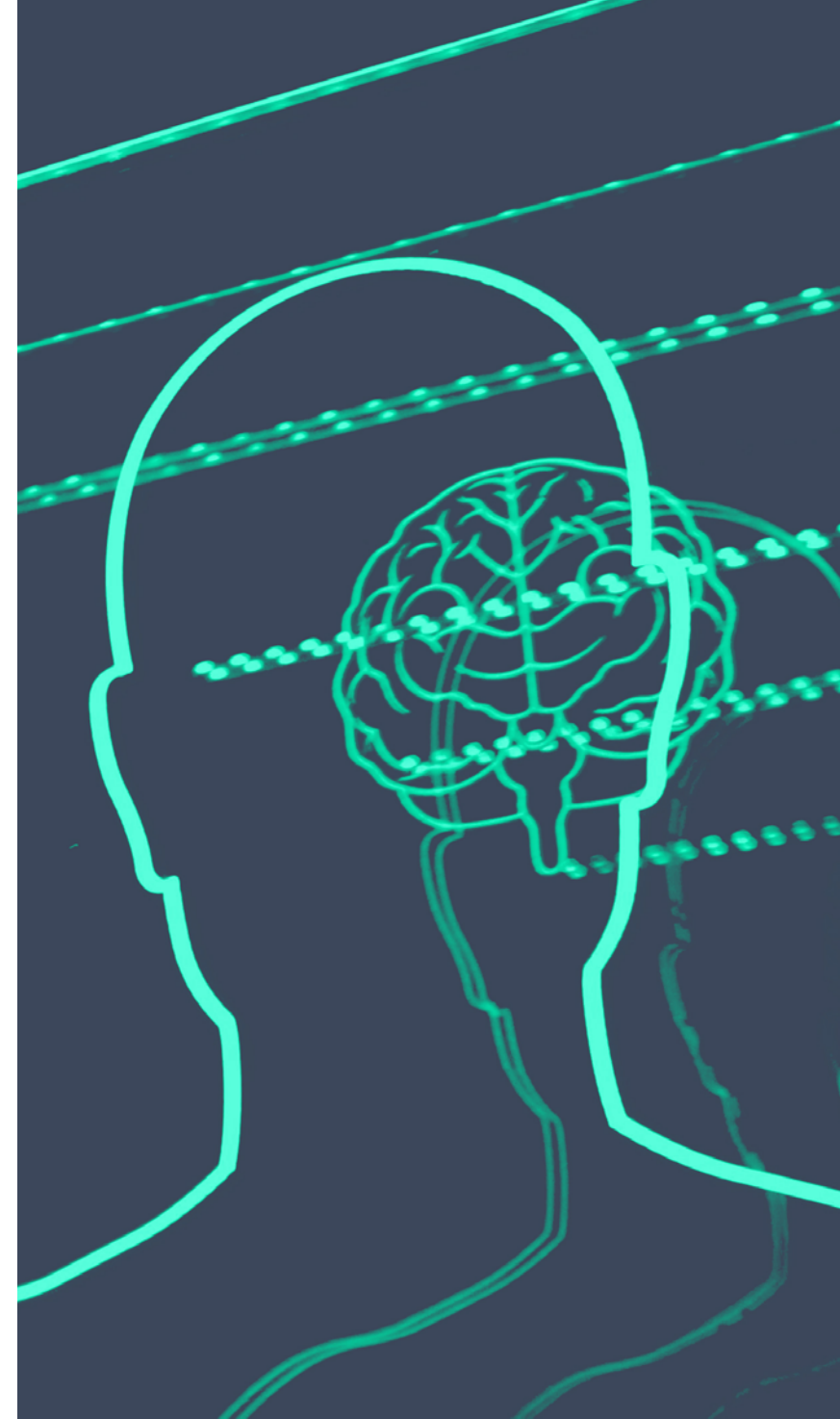
A uniquely positioned antipsychotic awaiting FDA approval

Nuplazid, a drug developed by Acadia and approved for Parkinson's Psychosis, is awaiting an FDA decision in the near-term that could make it the first drug uniquely positioned to treat this patient population.

- Nuplazid demonstrated overwhelming efficacy in treating DRP. Its Phase 3 prevention significantly reduced the risk of psychosis relapse by almost 3-fold compared to placebo.
- There are ~800k patients in the U.S. currently receiving suboptimal treatment for their psychosis symptoms, representing a massive market opportunity.

* Drug used to treat a condition it is not approved for (not on the label)

**A warning about possible serious/life-threatening side effects



Industry-Wide Research Efforts

Immunotherapy leading the race

Antibody-based immunotherapy is the most advanced technique to treat AD by selectively targeting beta-amyloid (A β) aggregates in the human brain to induce their dissolution and degradation by the immune system.

- Biogen's aducanumab is currently awaiting the FDA's decision for approval, scheduled for June this year.
- Eli Lilly's donanemab, currently in Phase 2, has a similar mechanism of action as the aducanumab by targeting beta-amyloid plaques.

Using electricity to fight AD

Sending electrical pulses or applying magnetic fields seems to have positive effects on the treatment of Alzheimer's disease.

- Functional Neuromodulation, backed by Boston Scientific, just received FDA Breakthrough designation for their new deep brain stimulation (DBS) system targeting specific brain areas involved in memory.
- Cognito Therapeutics also received FDA Breakthrough designation for their non-invasive device which stimulates the brain at specific frequencies in order to activate the immune system for the degradation of A β aggregates.

Early diagnosis desperately needed

Although no biomarkers have been yet validated for AD, several potential ones are under investigation for their ability to help detect AD way before the first irreversible neurological symptoms are occurring.

- These biomarkers include abnormal levels of specific proteins in the blood, the cerebrospinal fluid (CSF), or in the urine.
- Early detection will allow for better control and prevention of AD.



An Ounce Of Prevention Is Worth A Pound Of Cure

Prevention is essential

Today, AD is diagnosed way too late, when the pathological symptoms have already occurred. There is a clear need to take action as early as possible to prevent the irreversible damages induced by the disease.

- Maintaining a healthy lifestyle including physical exercises and a specific diet is supposed to lower the risk of developing Alzheimer's, but it's not enough.
- Recent research and clinical studies showed that there are promising ways to prevent AD by acting on the microbiota or the immune system.

The microbiota and the brain

One hypothesis is that microbiota present in our gut or mouth is more closely related to the development of AD than we think, as we wrote in a [recent note](#). Acting directly on the gut microbiota and maintaining a good equilibrium in its population of micro-organisms seems a promising way to prevent the disease.

- Cortexyme, currently in Phase 2/3 clinical study, claims that AD is induced by *P. gingivalis*, a bacterium found in the mouth.

A vaccine to prevent AD

Vaccines activate the immune system in the brain to fight unwanted hosts but also bring risks associated with neuroinflammation and the irreversible damages that can result. New vaccines being developed for AD focus on minimizing this inflammation.

- Misfolded A β proteins are the potential target for the development of anti-AD vaccines.
- AC Immune, a swiss-based company, is currently in Phase 2 clinical trial for the development of an anti-A β vaccine.

SOURCE:

[AC Immune: Technology platforms](#)



Biogen – Blazing A Trail

The aducanumab saga

Aducanumab, a biological treatment developed by Biogen, has had everything but a conventional development and regulatory path.

- While the drug had positive Phase 2 results, Biogen ran 2 parallel Phase 3 studies, both were terminated for futility at an interim (earlier than planned) timepoint.
- But in a post-hoc analysis* the company announced that one of the studies showed a statistically significant effect and intended to submit the data for FDA's review.

A supportive FDA like (almost) never

Given the often-debated nature of the data, the agency's univocal support of aducanumab was unprecedentedly overwhelming. The advisory committee, however, was not on the same page.

- In their public review, known historically for being data-driven and critical, the FDA's scientists offered a major endorsement for approval of the treatment.
- However, the outside experts' panel review deemed the data unconvincing and voted unanimously against its approval.

A bell-weather for the entire industry

In their public comments, the agency has expressed its encouragement to look beyond the classical review process, given the high unmet need and failure rate. Approval of the drug following a negative vote would be a first in history and given the broad consequences from a public health perspective, could set a new watermark.

- In other words, the underlying message to the industry is that risks associated with not approving a drug that could be efficacious (and save lives) are greater than the risk of approving a drug that is safe but offers no substantial benefits.

* Post-hoc analysis is a statistical analysis that was specified after the data has been seen and could therefore be subject to biases.

• Biogen announced that the Phase 3 studies are unlikely to be successful and halts them

• Company announces efficacy in a post-hoc analysis, submits the drug application to the FDA

• FDA releases its briefing documents to the advisory committee, calling for approval

• The committee votes 10-0 against the approval

• Decision back at the FDA, agency not obliged to follow the committee recommendation

• Decision (PDUFA) expected 7 March 2021

Athira – An Emerging Player

Cautiously optimistic

Athira is developing a novel drug to treat AD that builds upon broad scientific findings and newly shaping regulatory framework for drugs in this indication. Athira's ATH-1017 is following a therapeutic pathway that is thought to play a key role in cell survival and regeneration.

- While this pathway is relatively well understood, its utilization for treating dementia is considered novel, and is therefore prone to an ever-higher burden of proof.

Looking beyond cognition

Athira's development plan is differentiated, encompassing validated biomarkers for neuronal health and drug activity to support evidence of cognitive benefit.

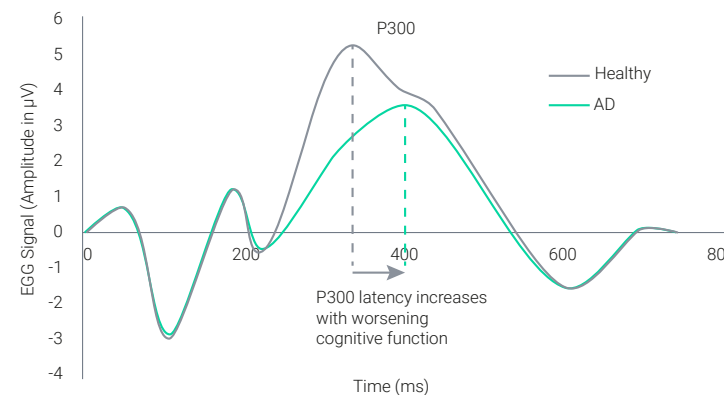
- The heart of their clinical strategy is P300 latency, a widely accepted measure for working memory processing speed that highly correlates to cognition.
- In a Phase 1 study with AD patients, the drug demonstrated a four-fold improvement* in P300 latency when compared to already approved therapies.

A huge opportunity

Several properties make ATH-1017 a potential biopharma blockbuster, notably that it is a self-administered injection, and that it is not expected to require MRI screening and monitoring, the main shortcomings of competing clinical assets.

- Before going generic, Aricept, a drug providing incremental cognition improvement, generated close to \$4bn in peak sales.

P300 LATENCY IS HIGHLY INFLUENCED BY AD AND OTHER DEMENTIAS



Drug	Population	Cognitive Impact	P300 Latency (MS)
Aricept	Alzheimer's	Improved	-16
Namenda	Alzheimer's	Improved	-15
Rivastigmine	Alzheimer's	Improved	-22
Scopolamine	Healthy	Decreased	14
ATH-1017	Alzheimer's	N/A	-73

*Cross study comparison, i.e., not head-to-head and with different timepoints.

Catalysts

- **Regulatory.** Potential approval of aducanumab could be a game-changer for Alzheimer's and dementia assets, by setting a precedent of a lower regulatory bar and potentially unlocking further growth.
- **Early-stage diagnostics.** Given its degenerative nature, early detection plays a key role in developing more efficient interventions.
- **Further clinical validation.** Additional treatment modalities including neuroinflammation, tau, and vaccines are advancing to clinical validation. Positive results could reignite interest in the space.

Risks

- **Clinical risk.** In Alzheimer's disease, patients' heterogeneity and lack of full understanding of the underlying biology have made this space susceptible to clinical failure.
- **New FDA commissioner.** With Biden taking office, a change at the top of the FDA is imminent, which gives some uncertainty about the accommodative approach of the agency towards AD.
- **False positive.** Approving drugs on inconclusive evidence that would turn out to be wrong could jeopardize the development of new treatments as patient recruitment would become more complicated.

Bottom Line

- Alzheimer's disease is one of the largest underserved public health conditions in modern medicine, and innovative treatments are urgently needed to enhance patient care and quality of life. The FDA has already made clear its stance by showing more flexibility on approving drugs in the space, and the aducanumab decision, if positive, could support a new wave of innovation.
- Medical innovations and regulatory developments could drive a transformational change in AD patient care. Our Biotech and Healthcare M&A portfolios are exposed to several players in this space.

Companies mentioned in this article:

Acadia (ACAD US), AC Immune (ACIU US), Athira (ATHA US), Biogen (BIIB US), Cognito Therapeutics (not listed), Cortexyme (CRTX US), Eli Lilly (LLY US)

CYBERCRIME TARGETING THE SUPPLY CHAIN

Hacked From Your Most Trusted Source

“The Weakest link” is now the least cyber-protected one

In the latest evolution of cyber-warfare, criminals are physically or digitally attacking a target by finding a weak point along its “supply chain”, e.g., hacking an email provider to spy on all its users.

- It is impossible to be fully protected from such attacks as it is essential to share information with the “supplier”, e.g., accounting, cybersecurity, data warehouse.

Damaging beyond the immediate costs

Supply chain (SC) attacks may be very efficient at damaging interconnected entities, given how the number of exposed end-points has increased due to globalization and outsourcing.

- The SC attack in December 2020 involved numerous U.S. federal institutions, including the National Nuclear Security Administration.
- The only way to mitigate the damage is to disconnect all affected hosts from the domain and rebuild them using trusted sources, resulting in sky-high fallout costs.

Mitigation is possible, real-time detection is necessary

The number of SC attacks increased >70% YoY. Cybersecurity requires complete control and observability of the whole network to ensure effective protection. Transitioning to the Cloud allows for this, and firms offering cloud-based services stand to benefit the most.

- Cybersecurity firms must offer automated forensic products, hunt down threats in real-time through the whole domain, and propose efficient damage control strategy in case containment fails.

SOURCE:
AtonRā Partners



Targeting The Weakest Link

Cybercriminals continuously search for entry points

It is hard to be 100% secure, as threats may come from any source. When hackers fail to target a company's network and systems directly, they may send malicious code via emails to vulnerable employees. Otherwise, they will search for weak entry points along the supply chain, significantly increasing the digital surface a company needs to monitor and secure.

- In the December attack, hackers initially exploited a vulnerability that Microsoft quickly remedied but then moved along the chain to the SolarWinds platform and put all its clients at risk.

Cyber-resilient systems

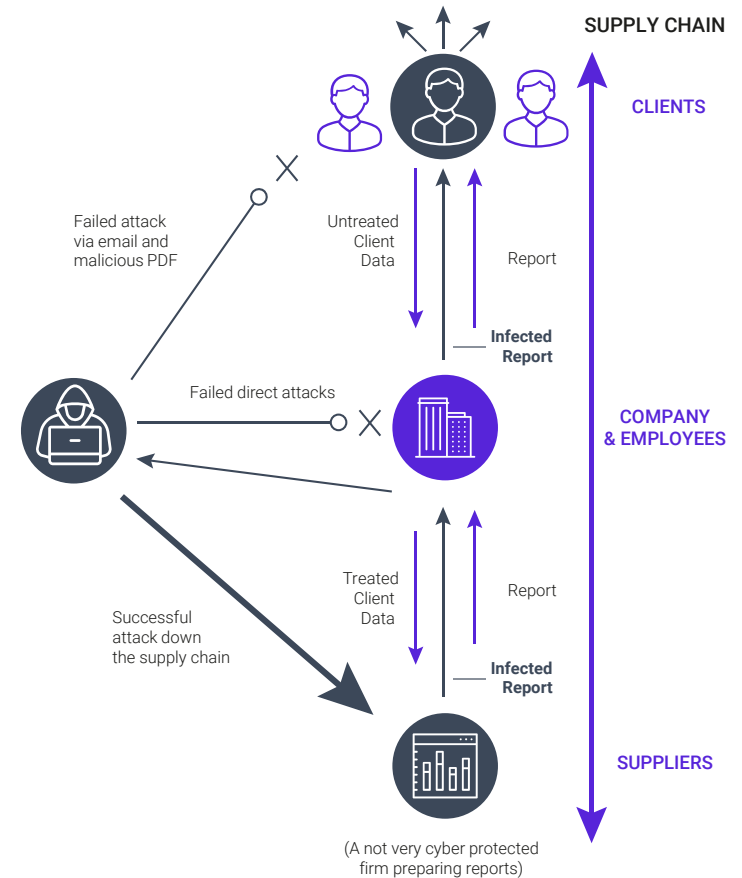
Protection from SC attacks starts by understanding the weak points in your network and building a cyber-resilient system, i.e., the ability to adapt quickly, contain, reboot, and self-repair in case of attack. Efficient protection needs to be coupled with fast-recovery processes to make a product offering stand-out.

- When the SolarWinds attack occurred, most of its customers had to completely stop operating for hours and days, rebuilding their systems.

Decreasing the risk of "human factor" is key

No matter the sophistication of security measures, the human factor remains the greatest risk, which is impossible to reduce to zero.

- Companies need to limit their supplier base to ensure more stringent controls.
- Conducting special cyber training and audits at suppliers' locations will ensure that all actors know and implement the latest cybersecurity recommendations.



SOURCE:
AtonRā Partners

Highly Damaging And Truly Far-reaching Attacks

The supply chain is only the first step

Often, it is not just one player that is targeted through the supply chain but the whole network. Attackers have adopted a U.S. military strategy, "Island Hopping", and aim at capturing as much cyber-area as possible.

- Employed by the U.S. Army in WW2, the strategy involved capturing separate islands to get to mainland Japan, e.g., Hawaii, Marshall, Guam.
- In cyberspace, disappointed by the data of one victim, attackers may decide to continue spreading further, using the first victim as their base of operations.

Supply chain attacks help to evade detection

By infiltrating a different endpoint altogether and being injected through a trusted partner's network, supply chain attackers can remain in a system for months. The relative ease in spreading across the network and "island-hopping" makes it an attractive criminal strategy.

- The high success rate of such attacks is the main reason why >80% of firms see an increase in SC attacks each year.
- Personal Health Information is the most sought-after data type.

Long-lasting consequences validate larger investments into cybersecurity

To spread, attackers are leveraging the brand name and trust that partners show towards the targeted entity. Successful attacks destroy both the brand name and trust that have been nurtured for years.

- Companies need to limit their supplier base to ensure more stringent controls.
- It is a no-brainer for companies to protect these valuable non-tangible assets by increasing their spending on cybersecurity solutions.

SOURCE:
Cyber-Security Insiders,
AtonRā Partners



Mitigation Is Possible, Detection Is Necessary

The best way to protect is to prepare

If the network gets exposed, the entity may contain the threat by having an incident response plan and a well-tooled team. The right tool is the one that offers an adequate level of visibility through the network up to every single endpoint.

- Teams should be maintaining the ecosystem's snapshot daily and train their ability to spot problems and be comfortable in navigating the entire network.

Improvements in the detection algorithm are needed

Current cyber systems verify traffic based on a malware database and geographical regions while detecting unusual settings. However, to detect supply chain attacks, systems need to use real-time behavior analysis to detect any abnormal deviations.

- Real-time analytics and visibility of networks are what cybersecurity players are heavily investing in.
- Cybersecurity firms need to offer real-time AI capabilities, leveraging their ability and speed to detect unwanted behavior and win customers.

Cloud facilitates observability and real-time control

The key benefit of the cloud is the real-time visibility and ease of observability. Cloud security firms scan the entire ecosystem, map all actors, quantify risk, and propose a way to reduce risk.

- More effortless scalability and a unified platform mean that no parameterization error is made during expansion, and all actors follow the same set of rules.

SOURCE:
Cyber-Security Insiders,
AtonRā Partners



Catalysts

- **Regular supply chain attacks.** Constant supply chain attacks will continue boosting the cybersecurity sector and spending on new solutions.
- **Cloudification.** As the world transitions to the cloud, it both requires and offers more cybersecurity with real-time observability and response.
- **Political instability.** Political tensions and transition from “armed” to “cyber” warfare would lead to more cyberattacks and investments into cyberspace.

Risks

- **Attacks similar to SolarWinds.** The recent attack exposed over 18k customers and decreased the cybersecurity firm’s value by more than 30%.
- **AI outsmarting security measures.** Malicious AI may be combined with a supply chain attack to mask the hack in real-time from cybersecurity systems.
- **A newer untraceable vulnerability.** Already being hard to detect, attacks injected via “invisible” vulnerabilities may remain in the system for years.

Bottom Line

- Cybersecurity and cyber response were dramatically inefficient and lagged the cyber threats in the past decade. Recently, supply chain attacks have entirely shaken the cybersecurity industry. With customers’ data lost, firms are looking for efficient ways to secure themselves.
- We believe the resurgence of supply chain attacks, in conjunction with “island-hopping” behavior, would boost the pace of innovation and be a massive catalyst for the cybersecurity market overall.

Companies mentioned in this article:

FireEye Inc (FEYE US), SolarWinds (SWI US)

MOBILITY SPACS ATTACK

SPACs Stealing The Spotlight

Boarding the hottest investment bandwagon

Recently, many electric vehicles (EV) and mobility startups have opted to go public through reverse mergers with Special Purpose Acquisition Companies (SPACs), to capitalize on the ongoing market enthusiasm for such deals.

- 26 mobility companies merged (or entered a reverse merger process) with SPACs in 2020, representing a combined valuation of >\$100bn.
- Merging with SPACs is a quick way to get listed, eschewing the long (and sometimes cumbersome) standard IPO process.

Separate the wheat from the chaff

In the mobility space, the various SPACs offer different value propositions. From companies that are already generating revenues through the sales of an existing product, to startups leveraging a concept, a few partnerships, and the promises of future profits. No wonder investors may be wary about what seems a market frenzy.

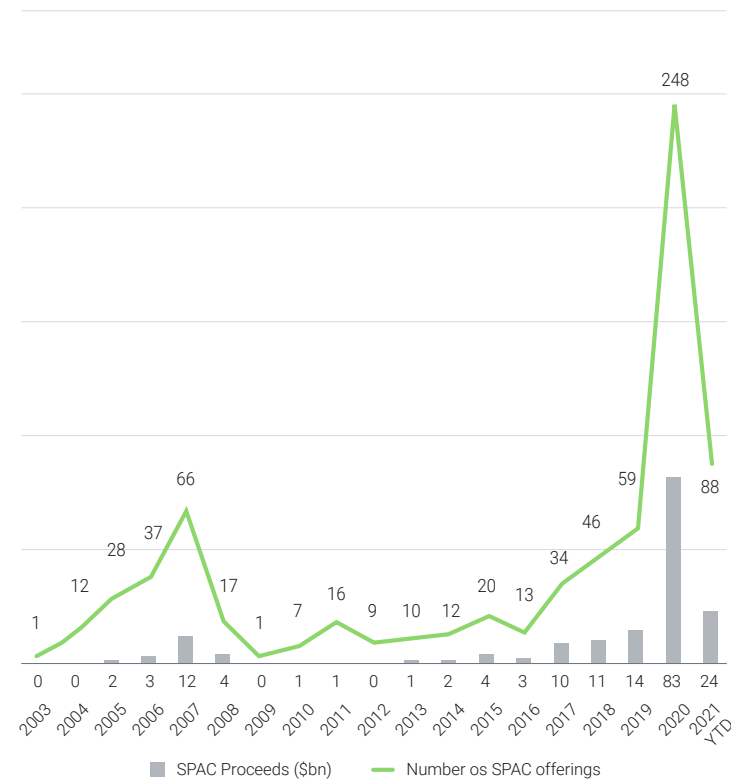
- Most EV-related SPACs do not expect revenues before at least 4-5 years.

Electric mobility remains a strong growth theme

The EV industry remains one of the fastest-growing sectors in our universe, driven by regulatory tailwinds, technological improvements, new model availability, and improving cost competitiveness. Even if things may be getting hectic on the SPAC scene, upside potential remains strong for the right players in the EV industry.

- The plug-in-hybrid and battery electric vehicles market is expected to grow from \$95.4bn in 2019 to \$415.4bn in 2025.

SPAC IPO VOLUME AND NUMBER OF OFFERINGS PER YEAR



SOURCE:

The EV/Mobility SPAC Handbook, PitchBook 2021

Electric Vehicles Poised to Reshape Auto Industry, PitchBook 2021,

<https://www.spacanalytics.com/>

The SPAC Mania

The year of the SPACs craze

2020 saw a surge in SPACs hitting the stock market, with some of the most notable ones being active in the electric vehicle and mobility space.

- More SPACs emerged in 2020 than in all previous 12 years together, and the SPAC-related volumes represented 46% of total U.S. IPO proceeds.
- Many of the SPACs that recently went public are focusing on high-growth and disruptive technologies, aiming for high market valuations.

An attractive route for companies

SPACs provide an easy pathway for companies willing to go public without having to cope with all the administrative hurdles and long delays of traditional IPOs. Many companies that struggled to raise capital in the private market eventually opted to use a SPAC merger and go public during the Covid-19 crisis.

- SPACs enable companies showcasing unproven technologies to raise money from public investors by selling growth stories based on their own projections.

Hitting the entire mobility value chain

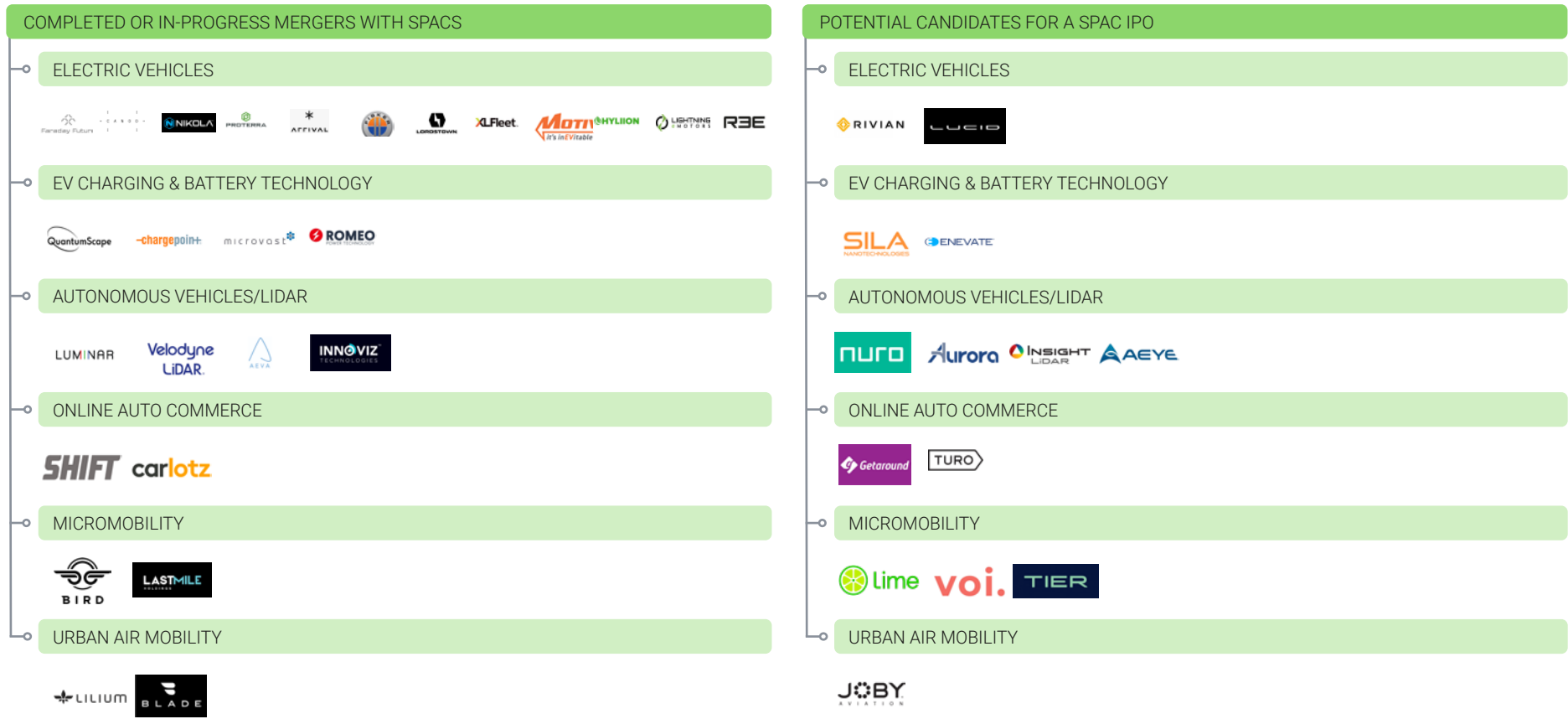
SPACs were involved with numerous mobility-related companies, covering the areas of next-generation batteries, charging infrastructure, electric vehicles at large, autonomous vehicles, micro-mobility, urban air mobility, and on-line auto commerce.

- Most notorious names include Nikola (fuel-cell and battery-electric trucks), QuantumScape (solid-state batteries), and Luminar (lidar technology), all seeing their market capitalization skyrocket above the \$10bn mark.

SOURCE:
The EV/Mobility SPAC Handbook, PitchBook 2021



Mobility Tech SPAC IPO Landscape



SOURCE:
The EV/Mobility SPAC Handbook, PitchBook 2021

Don't Fall For The Hype

The Robinhood effect

Retail investors were confined to their home with easy access to the stock market, stimulus money to splurge, and keen on making super-fast profits. Thus, very easy to get caught into a frenzy for hyped stocks where brand perception is favored over the company's fundamentals. As a result, the valuations of SPACs that haven't even yet delivered on their promises have gone ballistic.

- Nikola's market value neared \$30bn last year, thanks to a combined SPAC and hydrogen hype effect, without having yet built a single hydrogen-fueled truck.

Legit businesses exist too

Even in this SPAC mania, there remain a few legit companies with solid fundamentals and realistic goals. Such companies often already have a competitive product in the market or are working on disruptive technology.

- ChargePoint has one of the world's largest EV charging network with >150'000 charging stations.

Due diligence remains key

Sticking to fundamentals as well as carrying deep and rigorous due diligence on companies remains the best compass to navigate such stormy waters. Avoiding useless risks is key to remain in the game.

- Identifying potential risks and assessing their impact by looking at companies' track record, including management and board, past litigations, deal history, networks, knowledge on the sector, etc.

SOURCE:
SPAC Due Diligence What Really Matters and Why, Exiger 2020



Big Opportunities Remain

Penetration rates remain low

Despite the general enthusiasm around electric vehicles and related technologies, market penetration remains very low and most of the growth is still ahead.

- In 2020, electric vehicles represented less than 5% of all car sales globally, a share that is expected to reach 12% by 2025.
- Among all existing electric car models in the world, only five have already exceeded the 200k unit sales mark.

Improving driving range and charging times

Two of the traditional barriers to adoption, namely range and charging-time anxiety, are being overcome thanks to technological advances in batteries.

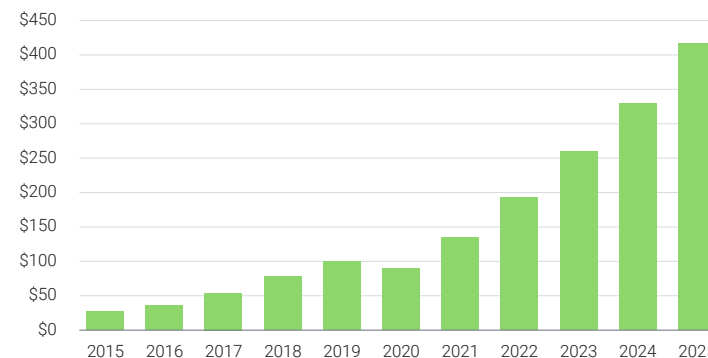
- Tesla is developing new battery chemistries and designs, aiming to improve energy density by 54% and reduce cost by 56%.
- Nio recently announced an upcoming 150kWh battery (likely to be supplied by CATL) made of ultra-high energy density solid-state cells, providing a driving range of more than 730km and a faster charge rate (80% in 15 minutes).

Supportive public policies

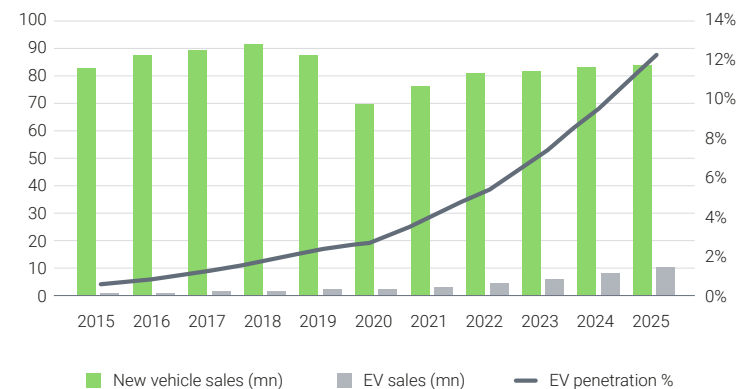
Favorable policies are impacting purchasing behavior and help accelerate the adoption of EVs on both the consumer and automaker ends.

- Following Biden’s election, GM announced its new goal of having all new light-duty vehicles to be zero emissions by 2035 as well as investing \$27bn in EV and associated products by 2025.
- Biden’s plan includes the installation of 500’000 public charging stations by 2025.

A >\$400bn MARKET OPPORTUNITY
ELECTRIC VEHICLES MARKET SIZE (\$bn)



ELECTRIC VEHICLE PENETRATION



SOURCE:
Electric Vehicles Poised to Reshape Auto Industry, PitchBook 2021,
Bloomberg New Energy Finance, Internal PitchBook Estimates | Geography: Global

Catalysts

- **Supportive regulations.** Existing government's commitments in phasing out new internal combustion engine vehicles (ICE) e.g., China, France, UK, Norway, etc., and potential new ones (e.g., U.S. to potentially ban ICE sales from 2035 onwards).
- **Market consolidation.** Innovative companies that went public through SPACs can be good candidates for acquisition from larger and well-established players in the EV space.
- **Technology breakthrough.** This wave of newcomers in the EV space could further accelerate the technology development in some key enabling technologies (e.g., batteries, charging infrastructure, etc.), hence accelerate market adoption.

Risks

- **Market overheating.** Overheating nascent technologies with cash could harm the underlying industry by providing a negative image to the sector in case of noisy failures.
- **Increased competition.** New actors on the market mean more competition for existing companies that have now to spend more resources to keep abreast of the competition.
- **Demand slowdown.** Lower-than-expected demand for electric vehicles (due to the pandemic or other factors) could punch the hyped valuations, with the risk of spreading across the entire sector.

Bottom Line

- Recent enthusiasm and market rally in the electric vehicle space has stimulated private companies' interest in going public through SPACs to capitalize on this trend. While many of the recent EV/mobility-related SPACs are only based on "promises and concepts", we believe that there remains significant upside potential for companies featuring strong fundamentals, competitive product lines, and solid business models.
- In our Sustainable Future portfolio, we seek to identify and invest in leading players that are best-positioned to capture the upcoming growth in electric vehicle sales.

Companies mentioned in this article:

CATL (300750 CH), ChargePoint (SPAC: SBE US), General Motors (GM US), Luminar (LAZR US), Nikola (NKLA US), Nio (NIO US), QuantumScape (QS US), Tesla (TSLA US), Velodyne (VLDR US)

CHARTS FOR THOUGHTS

Are Cryptocurrencies The Next Internet?

Undeniable parallels

In an interesting post a few years ago, Chris McCann presented the parallel evolution in terms of growth for cryptocurrencies and the (early) internet. For both, the growth curves show inflection points corresponding to wider adoption.

- The charts compare the '90-'95 (for internet) to the '13-'18 (for cryptos) periods.
- The exponential growth is well explained by Metcalfe's law on the network effect.

Users, assets, and funding

The charts show users, asset-base, and funding, even if data about cryptocurrencies is not as easy to measure as it was about the internet.

- Users' numbers are the hardest to estimate for cryptocurrencies.
- Asset-base growth is compared to the growth in the number of websites.
- Financing (adjusted for inflation) is probably the most comparable indicator.

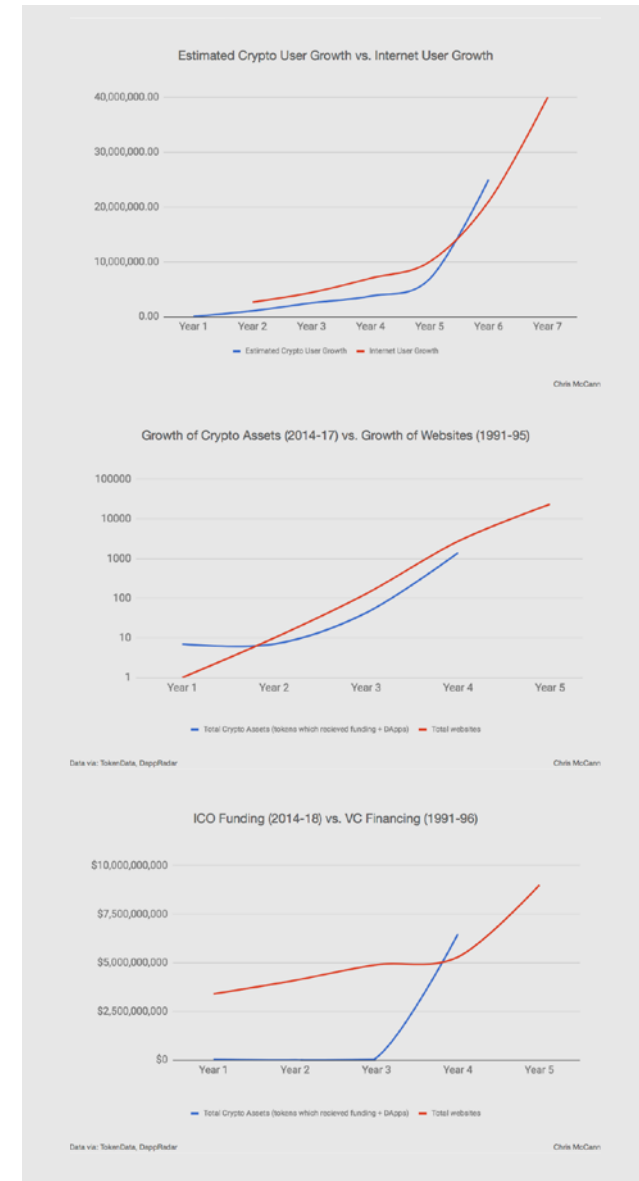
History does not repeat itself, but it rhymes

If history is of any guide, both the positives (structural, very long-term transformative nature) and the negatives (« irrational exuberance ») should be taken into account.

- Will the « winner takes it all » of the internet apply to cryptocurrencies? If so, which ones will ultimately succeed?
- How to separate the wheat from the chaff? What is purely hyped and what is going to transform the way we live and transact?

SOURCE:

[12 Graphs That Show Just How Early The Cryptocurrency Market Is](#)



Invest Beyond The Ordinary

Explore our investment themes:
www.atonra.ch/investment-themes/



HEALTHCARE
M&A



SUSTAINABLE
FUTURE



BIOTECHNOLOGY



AI AND
ROBOTICS



FINTECH



SECURITY
AND SPACE



MOBILE
PAYMENTS



BIONICS

About AtonRâ Partners

AtonRâ Partners is an asset management company, founded in 2004 with head office in Geneva, incorporated under Swiss law, duly approved by the Swiss Financial Market Supervisory Authority (FINMA) under the Swiss Collective Investment Schemes Act.

AtonRâ Partners is a conviction-driven asset manager combining industrial and scientific research with financial analysis. AtonRâ Partners focuses on long-term trends powerful enough to be turned into thematic equity portfolios.

Disclaimer

This report has been produced by the organizational unit responsible for investment research (Research unit) of AtonRâ Partners and sent to you by the company sales representatives.

As an internationally active company, AtonRâ Partners SA may be subject to a number of provisions in drawing up and distributing its investment research documents. These regulations include the Directives on the Independence of Financial Research issued by the Swiss Bankers Association.

Although AtonRâ Partners SA believes that the information provided in this document is based on reliable sources, it cannot assume responsibility for the quality, correctness, timeliness or completeness of the information contained in this report.

The information contained in these publications is exclusively intended for a client base consisting of professionals or qualified investors. It is sent to you by way of information and cannot be divulged to a third party without the prior consent of AtonRâ Partners. While all reasonable effort has been made to ensure that the information contained is not untrue or misleading at the time

of publication, no representation is made as to its accuracy or completeness and it should not be relied upon as such.

Past performance is not indicative or a guarantee of future results. Investment losses may occur, and investors could lose some or all of their investment. Any indices cited herein are provided only as examples of general market performance and no index is directly comparable to the past or future performance of the Certificate.

It should not be assumed that the Certificate will invest in any specific securities that comprise any index, nor should it be understood to mean that there is a correlation between the Certificate's returns and any index returns.

Any material provided to you is intended only for discussion purposes and is not intended as an offer or solicitation with respect to the purchase or sale of any security and should not be relied upon by you in evaluating the merits of investing in any securities.