Beyond Ardian: Lightstone's Contrarian Bet

That Big Investments in Early-Stage Devices Can Pay

by
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Early-stage investor Lightstone Ventures believes it can reap biotech-like returns on device holdings by tweaking the business model it uses to build its portfolio companies. By going deep on physiology, backing the science with strong data, and combining its choices with the ability to extract good deal terms at an opportune time, Lightstone expects to achieve high upside and comparatively early exits.

Broadly speaking (exceptions exist), venture capitalists' returns on medtech holdings trail those of their biotech investments by a very long shot – and the ability of venture firms to raise capital for their device funds reflects that. While the amount invested annually by VCs in the medical devices sector is roughly consistent, at about $2.5 billion a year, it is a shrinking proportion of total dollars spent on venture capital, totaling an estimated 6% in 2014, down from 10% in 2011, 9% in 2012, and 7% in 2013 (*see Figure 1*). In contrast, the biotech ratio is also down but not by nearly as much, and it constituted about 15% of all VC investing in 2013, according to a report by PricewaterhouseCoopers Consulting and Silicon Valley Bank (SVB).

That hurdle isn't stopping Lightstone Ventures (LSV) from making a bold play in the medtech field, with the ambitious goal of obtaining biotech-like returns on its device assets. Success would put its returns far above the sector's ten-year average of 6.8%, compared to 28.5% for biotechs, according to Cambridge Associates.

To get to that point, the two-year old firm, which is the brainchild of the former life sciences teams at Advanced Technology Ventures (ATV) and Morgenthaler Ventures, is focusing on early-stage, breakthrough device and biotech technologies. By going deep on physiology, in some cases addressing the same targets as drugs for particular diseases; backing the science with strong data gleaned from extensive studies; and combining its choices with the ability to extract good deal terms at an opportune moment in the space, Lightstone expects to achieve high upside and comparatively early exits.

Despite vast, rapid changes in the healthcare delivery system and tough reimbursement pressures, the major medical device players "still highly value innovation," states Mike Carusi, a general partner, who also continues as a general partner at ATV.

To make the math work, Lightstone's companies need to address big patient populations and markets with potentially big payouts. "You have to put a certain level of investment in these companies upfront and the market opportunity has to justify that amount," Carusi says. If they can generate compelling clinical data earlier (via European-based randomized clinical trials), the companies could be of interest to buyers even prior to receiving US FDA approval, he says. To do that right will require about $60 million to $70 million of venture funding. But if these firms can capture exits of between $500 million to $1 billion, compared to the more typical $150 million to $250 million, the rewards could be substantial.

"Strategics typically want to see if you can take share for next-generation products in existing markets, but what often happens is that the incremental benefit of these products do not outweigh the long-entrenched relationships they have with their customers. As such, it is very, very difficult to take share," he adds. "Our view is that breakthrough therapies in novel markets have the ability to attract strategic acquirers earlier because of their home-run potential. It looks like a biotech model in the device space."

Building on a Legacy

The motive for forming the firm came about when Morgenthaler and ATV independently, but at about the same time, decided they would move forward with smaller, separate IT and healthcare funds rather than raise larger, combined, balanced funds. This decision was driven by a belief that venture investing had become more specialized and that dedicated funds had the potential to outperform a blended approach. Both firms had previously raised $300 million to $400 million funds and had similar investment strategies.

Their common ground led Carusi and long-time acquaintance and Morgenthaler general partner Hank Plain to look for ways to pull their teams together. In 2012, the groups formed Lightstone, which in April 2014, announced the closure of Lightstone Ventures LP.

Given the sector's generally poor returns, the new fund "was not an easy story to sell [to LPs]," Carusi says; while the original goal was $250 million, the fund ended up with $172 million. Because medtech is out of favor with institutional investors, he adds, "We tried to reinforce that the strategy has worked for both ATV and Morgenthaler over the years and will continue to work for us, with tweaks and adjustments."

The plan is for Lightstone to invest 75% of the new fund in early-stage companies, split roughly equally between biotech and medtech, aiming at similar returns for each. The remaining money will be used to pursue later-stage assets, given emerging opportunities there, in part because firms created several years ago have not adequately adapted to changing buyer demands.

In biopharma, the sweet spot for investment will be in platform-to-product companies, while attractive device prospects will address "big opportunities with strong management teams," Carusi states.

A similar balance worked well for the legacy firms, although they put less emphasis on later-stage assets. Both, for example, were early investors in Ardian Inc. – Morgenthaler, along with The Foundry, seeded the company – and both reaped sizable rewards when **Medtronic Inc**. acquired it in 2010 for $800 million, plus earn-outs estimated at up to $500 million through fiscal year 2015. Ardian was in clinical trials with a catheter-based treatment for drug-resistant hypertension at the time and (despite recent problems during randomized clinical testing of its system), remains the device industry's current poster child for a successful early exit; total money invested in the company prior to the sale was $66 million.

Start-ups currently in the legacy portfolio, such as **Holaira**, **Kona Medical**, and **SetPoint Medical**, are structured along similar lines: development of a device that alters physiology to treat a common disease currently addressed by drugs and supported by a rigorous clinical development program that will generate enough positive data to position the

Figure 1

VENTURE INVESTMENT INTO DEVICE COMPANIES

	Device $ Invested ($ Billions)	$ as % of Total VC $ Invested
2007	$3.7	12%
2008	$3.6	11%
2009	$2.6	13%
2010	$2.5	10%
2011	$2.9	10%
2012	$2.6	9%
2013	$2.1	7%
2014*	$2.5 ⇧	6% ⇩

*projected

Source: Silicon Valley Bank

company for a potential early buy-out (pre-Phase III). Lightstone partners continue to manage these companies and ATV back-office operations support them. (*See sidebar "The Legacy Portfolio: Holaira's Big Bet on COPD."*)

Bigger Bets, Bigger Risks

But Lightstone's future ultimately rests with the portfolio it is building from scratch. Since its inception, it has committed money to five companies. These include three medical device companies: **EarLens Corp.** (hearing aid devices), **Claret Medical Inc.** (cerebral protection), and **FIRE 1** (Foundry Innovation and Research 1, Ltd, unofficially it is just Foundry IREland 1), and two biotechs (Catabasis Pharmaceuticals Inc. and Flex Pharma Inc.). (*See sidebar, "A Swing for the Fences with EarLens, a First-Mover Advantage for Claret." Also see "FIRE 1: A New Model for Early-Stage Device Incubation,"* The MedTech Strategist, *October 10, 2014*).

Just as their legacy firms did, Lightstone partners favor experienced management teams they have worked with previously. Fred Khosravi, chairman and co-founder of Claret Medical, and Lightstone partner Hank Plain were on several boards together, most recently Access Closure, which Khosravi also founded and which was sold in May to **Cardinal Health Inc.** for $320 million. EarLens Chairman, President and CEO William Facteau was previously head of Acclarent Inc., while Hank Plain was on Acclarent's board when **Johnson & Johnson** bought the maker of minimally invasive ear, nose, and throat devices, for $800 million in 2010. **Flex Pharma Inc.**'s Chairman, co-founder, and CEO Christoph Westphal, MD, PhD, had been backed previously by ATV in several ventures.

External pressures, however, are forcing Lightstone to tweak the old filters. Although the firm has not changed its ambitions at a high level in light of the challenging reimbursement trends and ever-greater barriers to market, it may "change the way in which we do things," Carusi says.

One alteration that the firm has embarked on is pursuing a geographically broad footprint. This globalization reflects a dramatic mindset shift for US VCs in general, who until very recently have kept their bases close to home, that is, in geographically tight clusters, where they could keep an eye on their portfolios and network with other entrepreneurs and engineers. The thinking was they needed to be near these groups to interact with their companies and maintain an up-to-date information flow. Lightstone's plans do not entirely jettison that idea – it still values proximity, but now that its operations are spreading out, so too is its base.

The Irish government's substantial investment in Lightstone's first fund underscores this point. Through Enterprise Ireland, an economic development agency and the National Pensions Reserve Fund of Ireland (NPRF), it contributed EUR30 million ($41 million), or nearly 25% of the total raised. In conjunction with the deal, Lightstone has opened an office in Dublin and plans to build out companies there. The office is headed by Lightstone partner Jason Lettmann and will serve as the firm's European headquarters. (*See "For Lightstone: A Faster, Less Expensive Exit,"* The MedTech Strategist, *October 10, 2014*).

The firm similarly is looking at initiatives in Asia for capital and also commercial opportunities, which it sees as having tremendous potential due to a greater self-pay burden. Several Asia-based investors are limited partners in Lightstone's fund, and while Carusi says their relationship is not as explicit as it is with Ireland, the Asian investors are "looking across the portfolio to determine if there are opportunities to commercialize the products in Asia."

In planning, the firm also talked to strategics, including Medtronic and **Covidien PLC**, which is domiciled there, about an Ireland-specific strategy. Tapping Ireland's resources, of course, is something many device manufacturers are doing; the country has a well-established device cluster and base of experienced engineering and manufacturing operations. It also has downstream tax advantages and allows strategics to tap overseas cash to make deals without incurring hefty US taxes. (See *"Medtronic and Covidien's $43 Billion Marriage: An Interview with Medtronic's Geoff Martha,"* The MedTech Strategist, September 22, 2014.)

"Strategics won't buy a company because it is domiciled in Ireland, but all other things being equal, this feature, coupled with the fact that many companies already have manufacturing and R&D operations there, will make that acquisition look more attractive, so why not have our operations there?" Carusi asks. "It [integration] could be cheaper for them and a factor in their deal valuations, and we would hope to extract some of that value."

In addition to Ireland's contribution to Lightstone Ventures LP, the country offers a European foothold through which it can team up with local venture firms, some of which are constrained by sovereign funds that invest in them to maintain a certain percentage of their holdings in EU start-ups. Their willingness to work with Lightstone is important because, with fewer VCs in the US focused on early-stage device investments, forming syndicates is tougher, putting greater pressure on the original investors to look for other sources of sustainable financing through long development cycles. Says Carusi, "We have to look for a whole new group of friends and to think creatively about new sources of capital."

The biggest reason for Europe's growing importance to the Lightstone portfolio, however, according to Carusi, is the region's faster route to market because of the shorter times required there to get clinical trials going and regulatory approval. Like many US-based start-ups, Lightstone companies (and the legacy portfolio it manages) already do their early-stage and feasibility studies in Europe, and often get their first approvals there. Those efforts are now laying the groundwork for expanding the amount and kinds of data the firms collect, and to do that, the firm wants to be physically closer to the activities as they progress.

The top medical device manufacturers, which are coveted as buyers of its firms, are increasingly intolerant of risk at all levels – even as they step up demand for groundbreaking technologies. In response, VCs have to build companies that are more attentive to operational areas like quality and compliance systems. "Our customers do not want downstream surprises," Carusi says.

That said, getting approval earlier in Europe does not mean Lightstone companies will launch full scale in the EU, but it does mean that as they go for reimbursement on a country-by-country basis, they can continue to generate the data that strategics and others want. European launches are idiosyncratic, with tactics dependent on the product and country. A next-generation iteration of an existing technology that already has reimbursement in place could merit an aggressive launch, but a novel device product requires market development. In such cases, a controlled market release, in which companies methodically lay the foundation for growth is likely more appropriate and, if done properly, can create considerable value as companies advance their products, Carusi adds.

Although digging deep into the data – regardless of whether it's for reimbursement, real world analysis, or other applications – creates additional risk, "if the data is bad in those other areas, we might as well know that now," Carusi says.

A Blue-Chip Contrarian

Lightstone's bet is contrarian, but it isn't alone, and the approach has many potential advantages. With so many VCs closing shop or stepping back from early-stage device programs, remaining firms have access to more deals on better terms – an advantage not lost on them, or the roughly half dozen other VCs still heavily involved in the space.

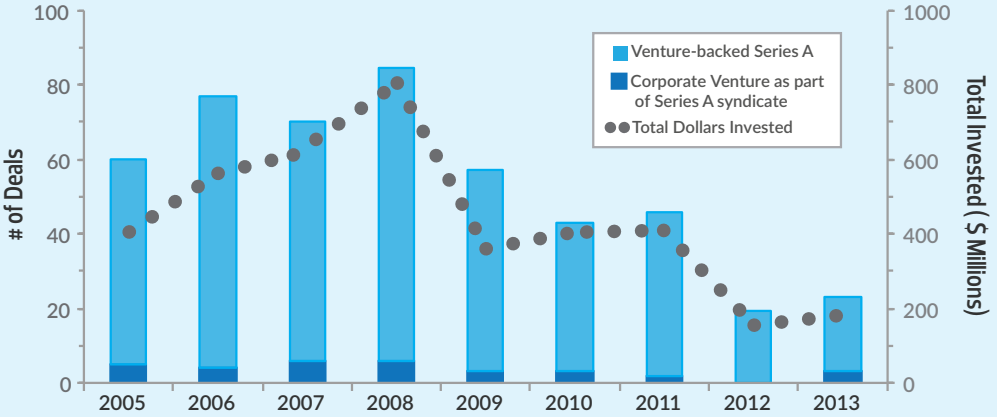
Moreover, Lightstone, by necessity or design, is open to learning from pharma's toolbox with a willingness to embrace creative deals that capture the value of early-stage assets while mitigating risk for both sides of the transaction. Deals involving earn-outs aren't new to the sector, but Lightstone's willingness to assume more financial risk as its companies go deep on science and physiology sets it apart from others. Lightstone is open to a variety of arrangements if that enhances strategics' willingness to engage sooner in early-stage bets at valuations the VC can accept. Such arrangements could include "build to suit" initiatives, for example, in which a company is developing a product for a specific strategic player, which in turn has an option to acquire the company for a predetermined amount downstream.

On the flip side, Carusi concedes that reasoning could break down if the companies do not sell in the right timeframe, leaving the VCs to fund the large US studies

Figure 2

DEVICE COMPANY CREATION

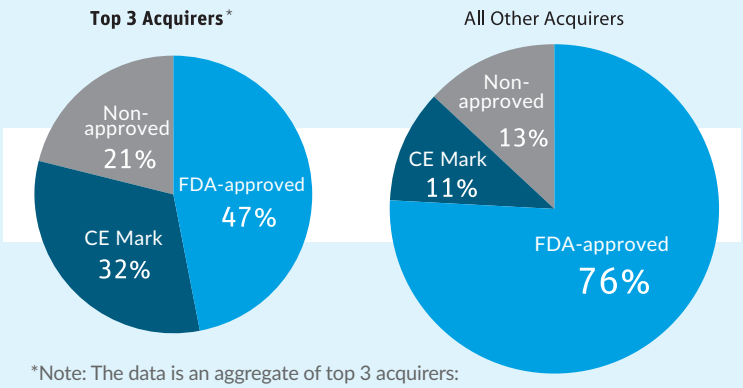
# of Deals and Total $$ in Series A



% of deals w/ a corporate investor	8%	5%	8%	7%	5%	6%	4%	0%	10%

Source: Silicon Valley Bank

Figure 3
BIG EXIT M&A BY STAGE AND ACQUIRER
2009-2013



*Note: The data is an aggregate of top 3 acquirers: Medtronic, Boston Scientific and CR Bard.

Source: *Trends in Healthcare Investments and Exits*, Silicon Valley Bank, July 2014

and the commercial ramp. Even so, VCs can still make solid returns, "but the multiples will start to compress," he says.

Because of the challenges of medtech investing, Lightstone is increasingly selective about its deals, with the result that it has set the first fund's deal volume goal at about 15, a more concentrated number of investments than its legacy portfolios.

And a lingering, important question is whether current health system economics really allow for high-priced technological innovation, even if it is a substantial improvement. In a world where purchasing discussion now revolves around whether to favor "good enough" as opposed to "state of the art," even truly – not incrementally – innovative products are getting tough to sell.

The hospital market into which the companies are directing their innovations is rapidly changing and facing tremendous financial and competitive pressures; in this environment, innovation will increasingly be defined by new technologies that, in theory at least, improve care and either do not add to near-term expenses or actually help to reduce system costs – for example, by transforming inpatient procedures into outpatient ones. Lightstone and other top VCs recognize this and say it is part of their planning. Yet, in reality such products are hard to come by; purchasing decision-makers, who are increasingly not physician users, are difficult to convince; and the mentality of "good enough" is permeating the buying culture.

Cost-saving technologies represent a new kind of innovation, but the problem is, they are such a radical departure from the way device start-ups and their VCs have thought about innovation that it's hard to get a handle on how to actually design for that kind of innovation. There are still hundreds if not thousands of legacy companies and projects that are built on the "incremental outcomes improvement" model and there's no real evidence right now that either strategics or public investors will reward companies who try a strategy defined as "we're all about system costs, not incremental improvements in outcomes."

Given all that, there is some sense, although not a certainty, that negative sentiment about early-stage investing may be bottoming out. Contrarians are gaining confidence since they believe that once the numbers move in a positive direction, investors will have missed the window. Series A numbers have been declining in volume and dollar amounts since 2008, with a big drop from 2011 to 2012, but there was a slight uptick in 2013, according to SVB (*see Figure 2*). The modest uptick appears to be holding for 2014, although it is too early to confirm, says Jonathan Norris, managing director at SVB.

That optimism also is driven in part by strategics' recent acknowledgement of their need for high-stakes innovation, even amidst the current intensive M&A bolstering scale and geographic scope. Both Medtronic and Covidien, for example, have said that their pending merger won't preclude them from seeking out small technology-driven deals, and Medtronic has said explicitly that a significant amount of the cost savings from synergies in the deal will go toward investments in start-ups and innovation, traditionally defined. (*See "Megamergers and the Evolving Medical Device Industry: Part II of our Interview with Medtronic's Geoff Martha,"* The MedTech Strategist, *October 10, 2014*.) Moreover, those deals are going to include early-stage assets, especially if that enables big companies to influence development.

Indeed, SVB's July 2014 report entitled "Trends in Healthcare Investments and Exits" states that more than 50% of deals done by the top three device dealmakers since 2009 were early-stage deals, defined as companies without FDA-approved products (*see Figure 3*). "We are not doing this in a vacuum, we deployed the strategy at ATV and Morgenthaler, and we have reason to believe it will work," Carusi says. "Lack of competition, contraction in the space, and the need for innovation make devices a very interesting place to play right now."

The Legacy Portfolio: HOLAIRA'S BIG BET ON COPD

In total, the Lightstone partners have about 43 active companies in their portfolio, all but five legacies from Advanced Technology Ventures (ATV) and Morgenthaler Ventures. Many of the legacy companies are based around the same investment priorities that are driving Lightstone: a novel device differentiated by physiological impact and backed by rigorous scientific data, aimed at a large patient population.

Founded in 2008, **Holaira Inc.** is a big bet on pharma-like value proposition for a device – a theme that resonates in several other Lightstone legacy companies. Based on novel understanding of an underlying disease pathway, Holaira is developing a catheter-based system to treat chronic obstructive pulmonary disease (COPD) by quieting the overactive airway nerves in a treatment known as targeted lung denervation (TLD). The one-time minimally invasive bronchoscopic procedure opens obstructed airways to ease breathing and has the potential to enable long-term improvement in lung function.

The market is huge, even by drug industry standards, and certainly for devices. About 190 million people worldwide have COPD, including 15 million in the US. Some of the world's largest pharmaceutical companies depend heavily on revenues from their treatments for the disease, which are best-selling drugs that are inhaled once or twice daily. Other treatments for COPD, none as widespread, include pulmonary rehabilitation, oxygen administration, and surgical intervention.

The device affects the same physiologic pathway as some of the current drugs – and not by accident the company is designing its clinical development program to align with that of clinical programs built around mainstay pharmaceutical therapies. The device is targeted to people with moderate-to-severe COPD, the same population as those taking long-established drugs like Boehringer Ingelheim's *Spiriva*.

In September, Holaira announced it was presenting the first data from two early, open-label feasibility studies at the European Respiratory Society International Congress; a peer-reviewed publication on results will appear this fall in the journal *CHEST*.

Currently, the device is in a two-part, 160-patient Phase II randomized clinical trial in select EU countries, with an initial estimated completion date of May 2016. Typically, dosing levels for new devices are set preclinically in animals or on the bench and then adjusted during clinical trials as data is acquired. Holaira has preclinical data on energy levels for TLD, but what it terms a "Phase II" study is designed to methodically determine the optimal dosing or energy levels of the device and, in a second part, to compare outcomes between the most effective energy level of the device and a sham procedure. Even the use of the word dosing in the press release and elsewhere suggests a term associated with drug trials. "That is not typical of devices," says Mike Carusi, the Lightstone partner who is supervising the holding and one of two Lightstone partners who sit on Holaira's board (representing ATV and Morgenthaler, not Lightstone). "We're taking a more rigorous approach."

Sham-controlled trials are not the norm for Class III devices either, especially for what is essentially Phase II trials, but these types of trials are increasingly important for gaining the acceptance of medical societies and global payors, adds Dennis Wahr, MD, CEO and president of Holaira.

A Novel Understanding of Physiology

Holaira's ties to its partners run deep. The company's board is an amalgamation of The Foundry, ATV, Morgenthaler, and other venture partners, all of whom work together on various projects; Wahr and the board members have known each other for years. Foundry managing partners Hanson Gifford III and Mark Deem are venture partners at Lightstone, and Lightstone operating partner Hank Plain continues as a vice chairman of The Foundry. The Foundry, which incubated Ardian and several other Lightstone legacy companies, also nutured Holaira very early on; both Morgenthaler and ATV came in later, with Morgenthaler coming in first. The Foundry is also a partner in FIRE 1, one of Lightstone's initial investments.

Inevitably, drug companies have approached Holaira and are closely watching TLD's progress. Whether their intentions are strictly to monitor potential competition or to evaluate the treatment as potentially complementary to their portfolios is not clear, "but I assume it is both," Carusi says. One big question is whether the drug will be adjunctive to or replace drugs, a concern

that the European trial is exploring. "We are trying to explicitly understand and glean data from the clinical trial in Europe about the optimal dosing and what the treatment paradigm will be – whether it is adjunctive to existing therapy or a potential replacement for drugs," he adds.

To date, investors have put $60 million into the company, including a $42 million Series D, which closed in April and included ATV and Morgenthaler as return investors. While that would hardly be enough funding to get a drug targeting a big patient population through clinical trials, the partners' thesis is that if it can prove the physiology in the European randomized, controlled clinical trial, it could be an acquisition candidate, and the buyer would assume support of the pivotal US trial. "For big, white spaces with novel physiology, the strategics continue to covet those spaces," he says. "Not that many companies fit that description and therefore there is potential for those that do to get acquired early."

Betting so heavily on physiology based in-depth data may be necessary but it is also risky, as both the drug and device worlds know. Ardian, the poster child of a great early-stage device exit, is also an example of how big bets can falter. The principal of interrupting nerve pathways to treat diseases ran into a roadblock in January, when Medtronic disclosed that its Phase III, randomized, sham-controlled trial of its renal denervation device for drug-resistant hypertension – which it added to its R&D portfolio when it acquired Ardian in 2011 – did not meet its primary endpoints. Medtronic has blamed the negative results on poor trial design and said it is evaluating next steps, but the trial outcomes surprised and shook the field, and disrupted some competitive device development plans. Still, the industry's optimism about denervation both for hypertension and other diseases remains strong.

–Wendy Diller

A SWING FOR THE FENCES WITH EARLENS; FIRST-MOVER ADVANTAGE FOR CLARET

***EarLens** and **Claret Medical Inc.**, two of Lightstone's recent medical technology investments, reflect different aspects of its investment strategy. (FIRE1, a joint venture of Lightstone, NEA, The Foundry, and Covidien, was profiled in the October 10, 2014 issue of* The MedTech Strategist.*)*

EarLens is developing a hearing aid that uses light to transmit sound, improving the quality and range of hearing. The device consists of a light-based sound processor that sits behind the ear and picks up sound and converts it to infrared light. The light carries the sound to a removable, custom-made box-like structure put in place near the base of the ear. The box, or Tympanic Contact Actuator, converts the signal into vibrations that are fed into the eardrum and produce sound (*see Figure 4*).

It's an atypical investment for Lightstone, given that the start-up has been in business since 2005, and hearing aids are paid for out-of-pocket. The device, however, has the potential to perform better than any device on the market, argues William Facteau, the company's CEO, president, and chairman. The self-pay aspect takes the reimbursement challenge off the table – although EarLens will have to find ways of making the product affordable to patients.

EarLens was founded by otologic surgeon-entrepreneur and Stanford University School of Medicine professor Rodney Perkins, MD, who has a long history of working on hearing impairment solutions, including co-founding **ReSound Corp**.

EarLens researchers spent years applying computational and statistical modeling to better understand the role of light in transmission of sound waves. The models were "very sophisticated and done by PhDs, but it was a different kind of work than normally happens in device companies," Facteau recalls; a 13-patient feasibility study eventually confirmed that the modeling correlated with clinical results.

Facteau, who joined the company in 2013 when it was still backed by angel investors, has built infrastructure and implemented a business plan. It was his opt-in that convinced Hank Plain and Mike Carusi of Lightstone, along with other professional investors New Enterprise Associates and Aisling Capital, to back the company.

EarLens previously raised close to $10 million from more than 70 angels and corporate investor **Medtronic Inc.** Earlier this year, it raised $38.8 million in a Series B round, which closed out an $8.5 million bridge and raised $28.5 million in new money, bringing the total funding committed to the firm to date to $50 million.

Lightstone and others had been watching EarLens, but "bringing on Bill was a game changer for us and paved the way for the company to do a full Series B," recalls Carusi. While the institutional investors didn't get in at the very onset, they are in agreement on the strategy going forward.

Figure 4

LIGHTSTONE VENTURES DIRECT INVESTMENTS

(as of Oct. 2014)

Company / Date Founded	LSV Investment Stage	Amount $$	Lead Investors	Date of Latest $$ Round	LVS Partner on Board	Technology	Product	Disease	Status of Product
Claret Medical Inc. 2009	Series B	Up to $18 M	Sante Ventures	Aug. 2014	Hank Plain	Filter-based cerebral protection systems for debris shed by a range of endovascular procedures	*Sentinel CPS*	Repair of structural heart defects	1st CE mark in EU in 2012; in pivotal trials for additional indications in the EU; beginning a pivotal trial in US
EarLens Corp. 2005	Series B	$40 M; prior to this financing, EarLens had raised $10 million from angel investors and Medtronic	Lightstone Ventures, New Enterprise Associates, Aisling Capital and undisclosed corporate investors	Feb. 2014	Hank Plain	Uses sound processor that picks up sound and converts it to infrared light, which carries power and sound to an implanted removable device at the base of the ear canal. The device converts this into vibrations that are applied to the eardrum	*EarLens Contact Hearing Device*	Hearing impair-ment	In US pivotal trial with plans to file for FDA 510 K approval by year end
FIRE 1 2013	Series A	$4.1 M	Lightstone Ventures, Covidien, New Enterprise Associates, The Foundry	Jan. 2014	Jason Lettmann	NA	NA	NA	NA
Flex Pharma Inc. 2014	Series A	$38 M	Longwood, Bessemer, EcoR1 Capital, Alexandria Equities, etc.	Sept. 2014	No	Ion channel activator	*FLEX 767*	Neuro-muscular disorders	To enter 3 large, randomized clinical trials 1st half 2015
Catabasis Pharmaceuticals Inc. 2008	Series B*	$32.4 M	Lightstone Ventures (returning investors: ATV, MedImmune Ventures, SV Life Sciences, Clarus Ventures)	Nov. 2013	Jean George**	SMART linker conjugate technology platform	Several drugs in clinical development of which furthest is CAT-2003	Inflam-matory and metabolic diseases	CAT-2003 in Phase II for hyperlipidemia

*The Series A, raised in 2008, did not include Lightstone, and ultimately raised $47.6 million, bringing total raised to date for the company to $80M.
**Jean George is a general partner at Lightstone Ventures and ATV.

Sources: Company filings, interviews, Lightstone Ventures

Most recently, the company finished enrollment in a 50-patient pivotal study, which is being conducted in the US. After a four-month follow up, it plans to file a *de novo* 510(k) with FDA by year end. While the scale of the clinical program seems small compared to those underway at other companies under Lightstone's umbrella, it is far more rigorous and larger than that done by most hearing aid manufacturers, Facteau says. "There is not as much data required for companies involved in hearing aids," he adds.

Lightstone invested in Claret in August as part of a Series B round led by Sante Ventures, which raised up to $18 million.

For air conduction hearing aids, the current standard of care, FDA requires certain performance standards and bench testing, but not clinical trials.

The timing of the data release from the pivotal study depends on the peer review process, but is likely in the spring. The company also plans to beta-test the product in the real world beginning in September.

In addition, the VCs insist that the company provide long-term data on performance and safety and the impact of hearing loss on cognition, which they deem necessary for sufficient reimbursement and stakeholder support.

Claret: A Later-Stage Opportunity

Claret is a different kind of investment, representing Lightstone's steady interest in later-stage opportunities that offer faster paths to revenues and offset the risk of early-stage, disruptive technology plays.

Founded in 2009, the company makes a percutaneous cerebral embolic protection device that captures and removes debris during transcatheter aortic valve implantation (TAVI; also known as TAVR) and other endovascular procedures. The third-generation *Sentinel EPD* received marketing authorization in Europe in December 2013 and has been used in more than 800 procedures worldwide.

Claret is an opportunity to grab a first-mover advantage in a competitive market. "The combination of an elegant and innovative technology, a battle-hardened management team, and a rigorous, focused clinical development program that includes proof of efficacy from ex-US studies and a high-quality randomized trial in the US, will likely culminate in the first commercial cerebral protection technology for TAVR, leapfrogging other participants in the space," says Carusi. "If the data is positive in the US pivotal trial and consistent with recently unveiled European clinical data, it will be compelling for doctors, the FDA, and therefore strategics."

Claret's technology is differentiated from the competition by its small size, ease of use, and ability not only to capture debris but also to remove them from the circulation, Carusi says.

The company released outcomes data from its CLEAN-TAVI trial, the first randomized, controlled trial (RCT) of its kind at the Transcatheter Cardiovascular Therapeutics (TCT) meeting in September, and most clinicians said that if the data presented there continues to hold up, "there is no reason why you would not do this," he adds.

Thirty-day results from the RCT comparing the device versus no cerebral protection showed a highly significant 53% reduction in total volume of new brain lesions in patients who were treated with the device versus those who were not. Moreover, patients in the device group also had a 60% reduction in the number of new brain lesions two days after the TAVI procedure and a much lower incidence of neurological symptoms of ataxia (9% in the treatment group versus 24% in the control).

Lightstone invested in Claret in August as part of a Series B round led by Sante Ventures, which raised up to $18 million. As with EarLens, angels funded what was essentially the Series A, so Lightstone was part of the first institutional round, and thus able to make sure the investors and company are all on the same page regarding strategy. Founder and Chairman Fred Khosravi has an extensive track record in successful entrepreneurship and has worked previously with many of the Lightstone partners.

Proceeds from the raise are being used to complete the US pivotal trial of *Sentinel*. The 284-patient multicenter, randomized, controlled trial, which launched in October, is designed to evaluate the role of the device in reducing the number and size of new ischemic lesions in the brain and their impact on cognition. Primary endpoints are reduction in total new lesions (as measured by diffusion-weighted magnetic resonance imaging) and major adverse cardiac and cerebrovascular events (MACCE). Secondary endpoints include neurocognitive and histopathological outcomes during TAVI.

–Wendy Diller