EDISON

Pixium Vision

Focusing in on Prima

Focus shifts to Prima as human trials proceed

Healthcare equipment & services

8 March 2018

Price	**€2.91**
Market cap	**€42m**

Pixium Vision is developing Prima, a potentially breakthrough wireless sub-retinal implant that generates electrical impulses at the retinal bipolar cell level to restore a form of central visual perception in patients with advanced retinal disease. While competing retinal implants generally target rare conditions involving near-total blindness, Prima seeks to address initially a larger unmet market indication, dry age-related macular degeneration (Dry-ARMD). Prima started human feasibility studies in late 2017 and could start EU pivotal trials in H119. Using a risk-adjusted NPV model, we obtain a pipeline rNPV of €77.4m, down from €82.6m previously.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/16	2.5	(12.4)	(0.98)	0.0	N/A	N/A
12/17	2.5	(13.5)	(1.02)	0.0	N/A	N/A
12/18e	2.5	(10.1)	(0.71)	0.0	N/A	N/A
12/19e	2.5	(20.9)	(1.44)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding amortisation of acquired intangibles, exceptional items and share-based payments.

Prima well-differentiated from epi-retinal devices

Prima could potentially offer sufficient improvements in visual acuity (VA) to provide benefit to patients with advanced Dry-ARMD. Animal data suggest Prima's current chip iteration could provide up to 8% of the VA seen by healthy persons. Over 500,000 US Dry-ARMD patients have VA below this level. In contrast, competing epi-retinal devices (such as Second Sight's Argus II) provide theoretical VA under 1%, limiting their applicability to rare retinal conditions that involve more profound vision loss. Another potential advantage of Prima is its miniaturised size (2x2mm) and wireless mode of operation which would enable a potentially shorter and less invasive surgical implantation procedure, as no trans-scleral wires are necessary.

Human studies now underway

Pixium recently began a five-patient Prima European feasibility study in patients with advanced Dry-ARMD. Pixium reported that the first two implantations and device activations were successful, as the affected patients reported light perception in the central visual field, where there had been none previously. Interim results are expected in H218 and may lead to the start of an EU pivotal study in H119. Implantations within a US feasibility study programme will start in Q218.

Valuation: €5.44/share including €1.4m YE17 net cash

We apply a risk-adjusted net present value (rNPV) approach, with a 12.5% cost of capital. Given recent advancements in human trials, we raised our probability of success estimate for Prima to 15%, from 12.5% previously. We have also removed Pixium's earlier generation Iris II product from our valuation, given a recent decision to halt its further development. After pushing our EU launch estimate to H122 (from 2021), raising our European pricing assumptions, adjusting for FX changes and rolling forward our estimates, we now obtain a pipeline rNPV of €77.4m, down from €82.6m previously. After including €1.4m in net cash at YE17, we obtain an equity valuation of €78.8m, or €5.44 per share.

Net cash (€m) at 31 December 2017	1.4
Shares in issue	14.5m
Free float	24%
Code	PIX
Primary exchange	Euronext Paris
Secondary exchange	NA

Share price performance

%	1m	3m	12m
Abs	(9.1)	6.2	(58.5)
Rel (local)	(8.1)	9.5	(60.9)
52-week high/low		€7.3	€2.5

Business description

Pixium Vision develops bionic vision systems for patients with severe vision loss. Its lead product, Prima, a wireless sub-retinal implant system designed for Dry-ARMD, is already in human feasibility study in Europe and expected to start US feasibility study in Q218.

Next events

Start recruitment for US feasibility study	Q218
Interim data from EU feasibility study	H218

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Investment summary

Company description: Restoring sight to Dry-ARMD patients

Pixium Vision was founded in France in 2011 and initially raised €24.3m in venture funding. It then raised €39.5m in its IPO in 2014. The firm purchased Iris epi-retinal implant assets from Intelligent Medical Implants in 2012 for €11m, and initially worked on advancing this device for severely blind patients with retinitis pigmentosa (RP). Pixium has also developed and now shifted its focus to a more advanced sub-retinal implant, Prima, which was developed in conjunction with Stanford University. The Prima platform, with its scalable design, is theoretically capable of approaching facial recognition levels of VA and as such is being advanced for the much larger and currently unmet market need of patients with severe vision loss from advanced atrophic Dry-ARMD. A feasibility study in Europe started in late 2017, with interim data expected in H218. Recruitment and implantations for a US feasibility study will start in Q218.

Valuation: Pipeline rNPV of €77.4m

We value Pixium using an rNPV approach, applying a 12.5% cost of capital. Given the successful activation of Prima in the first two implantations of the EU feasibility study, we raised the probability of success estimate for Prima in our model to 15% (from 12.5% previously). Pixium halted further development of its previous-generation Iris II epi-retinal implant directed towards RP, and we have removed this project and the associated costs from our model. Our valuation is now entirely based on the Prima opportunity in atrophic Dry-ARMD, in the EU and US geographies. We pushed back our EU launch forecast to H122 (from 2021 previously), raised our average European pricing assumptions and adjusted our FX assumptions. After rolling forward our estimates, we now obtain a pipeline rNPV of €77.4m, down from €82.6m previously. After including €1.4m in net cash at YE17 (€10.5m gross cash minus €1.5m in conditional advances and €7.6m in long-term debt), we obtain an equity valuation of €78.8m, or €5.44 per share (compared to €6.58, previously).

Financials: Funded through Q119, more capital needed

Given Iris II development has been halted, we have lowered both our R&D and G&A spending forecasts and we now project 2018 and 2019 cash burn rates (excluding net interest) of €7.3m and €17.3m, versus our prior estimates of €13.6m and €24.9m, respectively. We continue to expect R&D costs to rise y-o-y in 2019 due to costs associated with Prima clinical studies. We expect Pixium's gross Q417 cash of €10.5m, plus up to c €6m available through an equity facility (of which approximately 50% had been exercised since YE17), should support its runway through Q119. Given the reduction in our burn rate assumptions, we have lowered our expectations for Pixium's financing needs in coming years. Whereas we previously anticipated the firm would need to raise €15m in 2018, €30m in 2019, and €40m in 2020, we have now lowered our funding requirement projections to €10m, €20m, and €30m, respectively. We also expect Pixium to raise €25m in 2021. For illustrative purposes only, we have added our forecast funding requirements to long-term debt.

Sensitivities: Regulatory, commercial and funding

Much development risk lies with Prima as it has only recently begun to be tested on humans and in vivo longevity has not been proven. Further, the visual improvements offered must be sufficient to persuade patients and insurers to cover the implant, and be competitive vs potential emerging alternatives. Pixium will also depend on maintaining access to additional capital to fund Prima development. While our model accounts for these financings as long-term debt, the firm may have difficulties raising funds or need to issue equity instead, and there is a potential risk that pricing is not favourable for current shareholders, which would lead to significant dilution.

Company description: New-generation retinal implant

Pixium Vision is a French medical device company, which is advancing a retinal implant, or bionic vision system (BVS), that aims to provide a new form of vision to those with profound vision loss attributable to retinal diseases. These diseases permanently damage photoreceptor cells and impair their ability to translate visual stimuli into electrical signals transmittable into the optic nerve. The BVS intends to replace the signal processing functions of damaged photoreceptors by electrically stimulating other healthy retinal cells. These cells would then transmit the information towards the brain via the optic nerve.

Having brought its initial BVS, the Iris II epi-retinal[1] implant, to CE Mark commercial stage in 2016, with market access innovation reimbursement in Germany and France, Pixium is now directing its attention to its new generation Prima BVS. Prima is a tiny wireless sub-retinal chip powered by near-infrared light which delivers the electrical impulses at a more upstream level in retinal signal processing than epi-retinal devices, allowing a more natural neural network mediation of the information. This could potentially provide superior VA while involving a less invasive and time-consuming surgical technique. These attributes make it more suitable for the Dry-ARMD market, a substantially larger opportunity than the RP market targeted by Iris II, and currently without a proven treatment.

Prima sub-retinal device targeting ARMD market

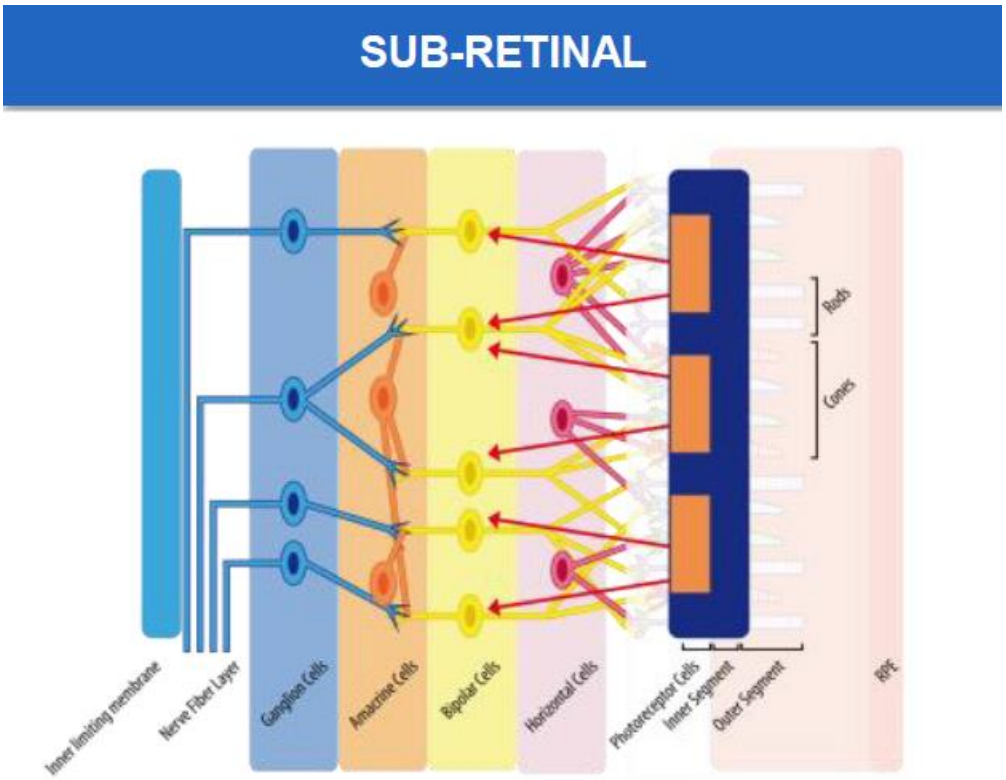
Prima is a miniaturised photovoltaic wireless sub-retinal implant that is implanted underneath the retina in a surgical procedure that may take less than 90 minutes under local anaesthesia. The current Prima iteration under human clinical development is a 2mm x 2mm wireless chip consisting of 378 electrodes (pixels) in total. Each photovoltaic pixel is independently controlled and self-powered by near-infrared light projected from goggles worn by the patient (the goggles consist of a camera and digital mirror projector, which emit a near infrared light pattern through the patient's eyes, designed to be processed by the Prima pixels). Located underneath the retina, the pixels embedded on the device aim to stimulate the patient's bipolar cells, which are located mid-stream in physiological visual signal processing. In normal visual function, photoreceptor cells (located on the outer portion of the retina, or closer to the choroid) send information to bipolar cells (located within the retina), which then relay information into retinal ganglion cells (RGCs, which are on the inner portion of the retina), and onto the brain through the optic nerve.

Fully wireless chip enables optimal sub-retinal placement

While epi-retinal implants (Pixium's Iris II and Second Sight's Argus II) reached commercial stages for advanced RP, a rare blinding disease, a sub-retinal wireless chip such as Prima can provide potential benefits such as a less invasive surgical approach. While the existing epi-retinal stimulate RGCs, the more biomimetic sub-retinal approach applied by Prima enables a more upstream level of interfacing in vision processing (by aiming to stimulate bipolar cells in the visual pathway).

1 Located at the surface of the retina.

Exhibit 1: Location of sub-retinal implant and intended communication with bipolar cell layer



Source: Company reports

Prima aims for a more physiological neural network mediation or natural image signal processing. By intending to stimulate first the bipolar cells (as opposed to RGCs), Prima leverages the retina's existing intrinsic physiological pathways, as bipolar cells require lower electric neural activation thresholds to elicit a perceptual response (compared to RGCs). Prima's proximity to the bipolar cell network and the independent electrical circuit design of each pixel are designed to enable precise control of the emitted electrical signals. As Prima is powered with near-infrared light, it does not require permanent trans-scleral wires or cables (as needed by the wired epi-retinal implant designs such as Iris II and Argus II). Prima's fully wireless approach aims to ensure a less invasive surgical procedure, while also mitigating the risk of potential long-term complications that can result from permanent scleral openings (a potential risk with wired epi-retinal implant designs).

Prima requires clear optical media to function effectively, so patients with significant central corneal scarring may be contraindicated (and cataracts would need to be removed prior to implantation).

Improved resolution opens door to larger Dry-ARMD market

Animal studies suggest the current Prima iteration in feasibility studies could reach up to 20/250 in VA in humans (reflecting 8% of the resolution seen by healthy individuals). This level could be sufficient to provide meaningful improvements and justify implantations in patients in late stages of Dry-ARMD, such as those with retinal scarring or geographic retinal atrophy reducing best-corrected VA in each eye to below 20/200. This is in contrast to the epi-retinal devices cited above, which generally currently only provide very crude vision, with the theoretical limit of the Argus II being only 4 degrees (corresponding to about 0.4% of the resolution seen by healthy individuals). This restrained resolution generally limits the device's applicability to candidates with more profound (or near-total) central and peripheral vision loss, such as advanced stages of rare retinal dystrophies (such as RP).

Preclinical studies clear way for human studies

Data studied on ex-vivo[2] blind primate retina confirmed that there are localised, pixel (location-specific) responses in the RGCs, following sub-retinal stimulation using a Prima prototype. Animal model thermal[3] and electrical safety studies completed in 2016 successfully showed that the system meets the safety thresholds for thermal and electrical safety requirements for the eye. Pixium also presented data[4] in autumn 2017 at The Eye and the Chip (TEATC) conference in Detroit, MI, where it had implanted a Prima prototype in 11 cat eyes, six pig eyes, and 19 monkey eyes, with the retina remaining attached at the end of surgery in 100% of cat eyes, 95% of monkey eyes, and 86% of pig eyes. The animals were exposed to multiple illumination powers, including pulsed near infrared light, and visual evoked potentials in the cortex (brain) of the animals demonstrated that they perceived a visual stimulus when the Prima was illuminated with pulsed near infrared light. After three months in vivo, the implant showed no degradation and after euthanasia, histology analysis showed no degradation or damage to bipolar or ganglion cells in treated animals compared to the control group.

Human feasibility studies underway in the US and in Europe

Pixium announced on 19 October 2017 that it received authorisation from the French regulatory agency, Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM), to start a feasibility clinical study on Prima. The study will recruit up to five patients with advanced Dry-ARMD. To be eligible for the trial, patients will be required to have a severe stage of atrophic disease, with a VA of 20/400 (5%) or worse, as well as no light perception in the foveal (central portion of the retina) region, and an area of central retinal atrophy of at least 3-disc-diameters (approximately 5mm in length).

The study will be conducted at Fondation Ophtalmologique Rothschild and Hôpital des Quinze-Vingt in Paris with vitreoretinal surgeon Dr Yannick Le Mer acting as the principal investigator performing the implantations. Patients will be evaluated for safety and functional measures (including ability to elicit light-perception and VA) for 36 months, but interim data will be available at six, 12, 18 and 24 months as well. Pixium anticipates completing recruitment and all five implantations by mid-2018. If six-month data (anticipated in H218) is positive (showing some signs of visual perception or improved VA), Pixium plans to start an EU pivotal trial in H119 (consistent with our existing forecasts).

Pixium announced on 25 January 2018 the first human Prima implantation as part of the EU feasibility study, followed by its successful activation one month later (as per study protocol). Following activation, the patient reported light perception in the central visual field, where there had been none previously, and proceeded to the visual re-education stage of the study (to improve interpretation of the elicited light signals emitted by Prima). On 8 February 2018, Pixium announced the second successful implantation and activation. These successful activations are encouraging as an early suggestion of proof-of-concept that the device can interface with retinal cells to restore some visual perception. Additional implantations, as well as quantitative assessments of sustained visual performance and acuity at six months, can provide stronger validation of the technology platform and of its potential.

2 Living cells, but tested outside the host organism.

3 Lorach H, Wang J, Lee DY, et al. Biomed Opt Express. 2015 Dec 4;7(1):13-21. doi: 10.1364/BOE.7.000013.

4 Le Mer Y, Picaud S, Hubschman J, et al. Surgical and First Behavioral Test Results from the Sub-Retinal PRIMA Wireless chip implantations. Presented at TEATC conference 2017.

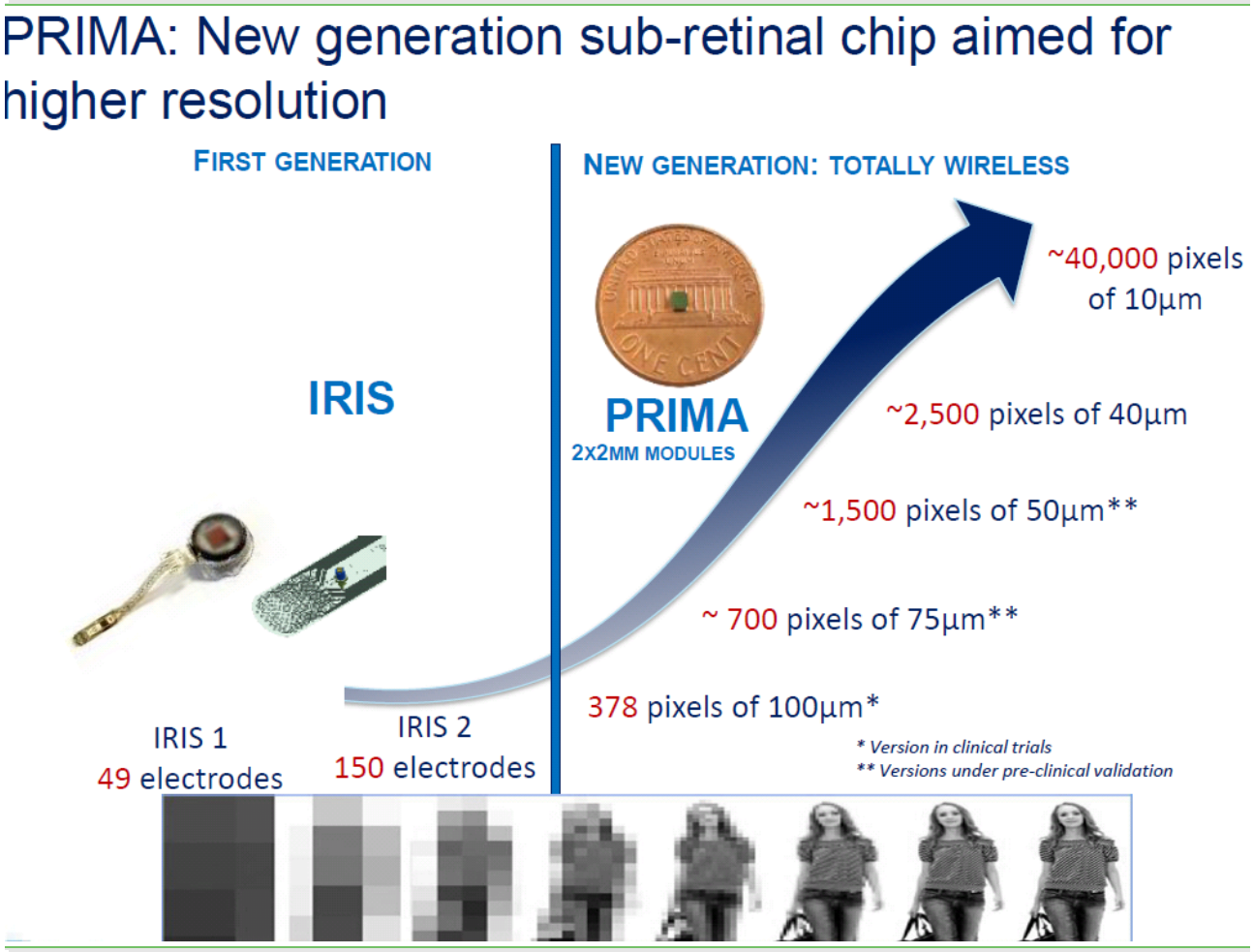
US feasibility study to begin in Q218

Pixium announced in early January 2018 that it has received approval from the FDA to begin a five-patient US Prima feasibility study under its breakthrough technologies programme, in patients with advanced Dry-ARMD. The study will be conducted at the University of Pittsburgh Medical Center. The primary end points are safety and restoration of visual perception at 12 months, with patients being followed for up to 36 months post-implantation. The first implantation could occur in Q218, and 12-month safety and performance data on all patients will likely be required before a larger US (pilot) study would be allowed by regulators. We anticipate that study data would be available in H219.

Future studies may involve higher pixel-density Prima chip

The current (initial) Prima chip iteration that Pixium is advancing in feasibility trials is equipped with 378 pixels (each pixel is about 100 microns in length and width). The company is already evaluating versions that use smaller and more densely packed pixels, potentially giving rise to Prima chip iterations with higher pixel densities. A 2mm x 2mm chip (same size as the current iteration) with pixels sized down to 10 microns could yield a chip with over 40,000 pixels. A higher pixel density (with single cell activation capability) may deliver signals with a higher level of visual resolution to the patient, theoretically up to even a level as high as 20/40 (50% of normal vision).

Exhibit 2: Scalable nature of Prima technology



Source: Company reports

We reiterate, however, that even if a Prima device can theoretically emit signals corresponding to a high level of resolution, the ability of the patient to resolve such fine details will depend on several factors, including:

- the integrity of the patient's retinal cell network;
- the ability of the brain to learn to interpret the new signals (hence the importance of the re-education phase);
- the precision in the communication between the Prima chip and the external projection transmitted by the glasses worn by the patient; and
- the efficacy and precision of communication and interfacing between retinal cells and the electrical signals emitted by the Prima chip.

Hence, it is currently premature to speculate even as to the level of resolution that the current 378-pixel iteration of Prima is likely to provide (other than it is unlikely to meaningfully exceed 20/250), or whether future higher pixel-density iterations would yield significant potential improvements in the level of potential resolution perceived by the patient (since such will depend on practical limits as to the maximum precision that could occur between the interfacing of the patient's neural cells and the signals emitted by the chip).

As the company works through the feasibility studies, it is conducting parallel preclinical work on higher-pixel density iterations, and it possible that future trials (eg the EU and US pivotal studies for Prima) could use higher pixel density devices than the current 378-electrode iteration. It is also conceivable that should a Prima iteration obtain approval, a follow-on device could be advanced with higher electrode densities and higher theoretical potential resolutions, which can potentially improve the level of VA attainable by the treated patient.

Regulatory strategy and timing review for Prima

The European regulatory strategy involves starting an EU pivotal study in H119, which we estimate will require 12 months of follow-up safety and efficacy data for European regulators to provide CE Mark approval. While CE Mark approval was attained for Pixium's Iris II using completed study data from only 10 implanted patients, Iris II was targeting a much more narrow rare/orphan disease market (RP and related rare dystrophies) and an existing predicate epi-retinal device (Argus II) had already been approved. For Prima, which is aiming to treat the demonstrably larger advanced Dry-ARMD market (late-stage ARMD's prevalence is over 6x higher than all-stage RP) and for which no comparable predicate device exists, we estimate that the EU pivotal study may require between 50-60 patients. However, the true size will not be known until the current EU feasibility study is completed, as the final recruitment size for the EU pivotal study will likely depend upon on the safety and level of visual improvement shown within the EU feasibility study. However, we reiterate that generally, to obtain CE Mark approval, product safety is the primary consideration for regulators (CE Mark approval generally does not require demonstration of long-term clinical efficacy). We continue to estimate that EU pivotal study data will be available in early 2021. However, due to the increasing scrutiny of European regulations for the review of Class III medical devices (the appropriate classification for a retinal implant like Prima), such as through the implementation of European Regulation 2017/745, we have pushed back our anticipated timeline for potential EU commercialisation (CE Mark approval) to H122, from 2021 previously.

The US regulatory pathway for medical devices is more comprehensive. Our expectation is that following the attainment of 12-month data from the current US feasibility study (which we anticipate in H219), a larger US pilot study would need to be carried on a larger number of subjects (we estimate approximately 30 patients in total) prior to the start of a US pivotal study. We estimate that US recruitment for this pilot study would start in H219.

Under an ideal scenario, Pixium could potentially also include data from sites participating in the EU pivotal trial as part of the US pilot study, which would reduce the need for duplicate or overlapping studies on similar patient populations. We assume this will be the case, thus allowing for the completion of the US pilot study in H220. We assume a US registration-enabling pivotal study would then start in H220, which we believe will likely require 60-80 subjects and 18-24 months of follow-up. Hence, we now assume the earliest possible date for US approval and launch will be H222 (in line with our existing forecasts).

Exhibit 3: Projected clinical development pathways for EU and US

EU clinical pathway	US Clinical pathway
Clinical studies needed	
1. Small-size (~5-pt) feasibility study	1. Medium-size (~30-pt) pilot study
2. Medium-size (~50-60pt) pivotal trial	2. Larger (~60-80pt) pivotal trial
Projected characteristics and requirements for pivotal trial	
6-12 months of follow-up data	18-24 months of follow-up data
Study must show product safety	Study must show safety and efficacy
Projected commercial launch timeline	
H122	H223

Source: Edison Investment Research estimates

Altogether, we expect that CE Mark clearance (and EU launch) would still occur 18 months earlier than US pre-market approval (PMA) and launch. We now model US approval and launch in H223 (from H222 previously).

Market opportunity for Dry-ARMD

ARMD is the leading cause of blindness in adults over the age of 55 in western countries, and is characterised by damage to the macular[5] region of the retina, leading to central vision loss. ARMD patients generally maintain their peripheral vision. While the exact pathophysiology is not fully understood, ARMD is believed to be caused by oxidative stress, mitochondrial dysfunction and/or inflammatory processes. There are two forms of ARMD: dry (non-exudative) and wet (exudative).

- The wet form is accompanied by exudative and neovascular changes, which can lead to macular scarring and more rapid vision loss. This form accounts for about 10-20% of ARMD cases, but prior to the usage of anti-VEGF (vascular endothelial factor) injection treatments, it accounted for over 80% of ARMD patients with legal blindness.[6]
- The dry form accounts for about 80-90% of cases and does not involve neovascular changes; cellular atrophy is the cause of photoreceptor damage. This condition currently has no proven treatment, although lifestyle factors and dietary or nutritional supplement changes may help slow progression. Prima is intended for instances of Dry-ARMD where there is significant central or macular retinal atrophy.

The prevalence of ARMD in adults above age 45 is estimated at 8.0% and late-stage ARMD (with best-corrected vision acuity of 20/200, or 10% or worse) affects about 0.4% of individuals in this age group.[7] This represents about 815,000 people in Europe and 517,000 in the US. We assume that 30% of this late-stage subgroup would have sufficiently poor central vision to warrant potential consideration for Prima, and that 30% of these would meet all remaining inclusion criteria (including having the dry form of the disease with significant central retinal atrophy) and/or be suitable as potential responders (ie this considers that many of the ARMD patients are in poor general health

5 The macula is the central region of the retina, containing the highest density of photoreceptors compared to other regions, thus accounting for the high level of resolution and colour perception associated with the central vision.

6 Legal blindness refers to patients with a central VA of 20/200 (10%) or worse in the better eye when a patient is wearing their best-corrected prescription lenses, or those with a visual field of less than 20 degrees.

7 Wong WL, Su X, Li X et al. Lancet Glob Health. 2014 Feb;2(2):e106-16.

and/or have concomitant eye diseases, such as glaucoma or poor optical media transparency, which would render them ineligible for Prima). Thus, we view the target ARMD treatment population for Prima as about 73,200 in Europe and 46,500 in the US.

Financial forecasts for Prima sales

Below we present our forecasts for Prima sales in Dry-ARMD. We have also adjusted our forecasts to no longer include RP sales forecasts for Prima. While we anticipate that Prima may eventually be used in RP as well as ARMD, we believe that pivotal studies in the RP indication would be needed prior to commercial implantations in RP patients (as we believe that Prima is unlikely to be deployed off-label for RP indications). We believe the firm's focus is on obtaining approval in the much larger Dry-ARMD market and hence, until the company is successful in obtaining approval in Dry-ARMD (in either EU or in the US), or unless it secures additional funding specific to advancing an RP Prima pivotal study, we believe the firm will not employ resources to develop Prima in RP. Hence, at this stage and until there are more definitive indications towards future development in RP, we believe it is more appropriate to remove Prima implantations in RP from our forecasts.

We have made several adjustments to our Prima forecasts in Dry-ARMD. We now anticipate launches in H122 in Europe (from 2021 previously) and H223 in the US (from H222, previously). To better take into account the time needed to secure optimal reimbursement and generate sufficient product awareness in the marketplace, we have also reduced initial volume sales on launch and lengthened the sales growth cycle. We now estimate it will take about five years to reach peak sales (for both the US and Europe), versus approximately three to three and a half years, previously. Given our view that patients with advanced stages of Dry-ARMD will have no alternative means to improve their eyesight should Prima reach commercialisation, and that there will be significant demand among affected Dry-ARMD patients to restore a form of central vision, we believe our prior market share may have been too cautious or conservative. We now estimate that the product will achieve a peak market share of approximately 7% (up from 5% previously) in those patients with severe atrophic forms of the disease and who meet all remaining inclusion criteria. Given discussions with management and considering the pricing levels that had been achieved with the initial European Iris II sales and that had been assessed through Pixium's Iris II discussions with reimbursement agencies, we have raised our initial average net (inclusive of any discounts or rebates) product pricing in Europe to €90,000 (from approximatively €80,000 previously), while maintaining our forecast for $150,000 in the US. Given this, and after applying our new FX assumption ($1.25/€ vs $1.18/€ previously), our peak Prima global sales estimate has increased to €1.013bn, but this has now been pushed back to the year 2028. We previously estimated peak global sales, occurring in 2025, of €671.5m. Our new 2025 global sales forecast is €534.2m.

Exhibit 4: Financial forecasts for Prima in Dry-ARMD

	2022e	2023e	2024e	2025e	2026e	2027e
Europe						
EU population (m)	518	520	521	522	524	525
Prevalence of late ARMD in >45 age group	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
Number of patients with late ARMD (000)	829.4	831.5	833.7	835.8	838.0	840.1
Late ARMD patients meeting all Prima eligibility criteria (000)	74.6	74.8	75.0	75.2	75.4	75.6
Prima unit sales in EU	366	1,282	2,532	3,814	4,879	5,288
Average revenue per treatment (€)	90,000	91,238	93,025	94,844	96,732	98,634
Total EU revenue (€000) for PRIMA-ARMD	32,899	117,010	235,542	361,751	471,933	521,540
United States						
US population (m)	342	345	347	350	353	355
Prevalence of late ARMD in >45 age group	0.4%	0.4%	0.4%	0.4%	0.4%	0.4%
Number of patients with late ARMD (000)	547.6	551.7	555.9	560.0	564.2	568.5
Late ARMD patients meeting all Prima eligibility criteria (000)	49.3	49.7	50.0	50.4	50.8	51.2
Prima unit sales in US	-	69	550	1,373	2,207	3,081
Average revenue per treatment ($)	na	151,950	154,167	157,073	160,147	163,335
Total US revenue ($000) for PRIMA-ARMD	-	10,556	84,859	215,603	353,443	503,189
Assumed $/€ rate	1.25	1.25	1.25	1.25	1.25	1.25
Worldwide total revenue (€000)	32,899	125,454	303,430	534,233	754,688	924,091

Source: Edison Investment Research

Iris II reintroduction on hold as firm focuses on Prima

Pixium's first BVS, the epi-retinal Iris II reached commercial stage, following CE Mark approval in July 2016 for the treatment of RP and other severe retinal dystrophies. A limited commercial launch was initiated, as longer-term follow-up within a 10-patient European clinical trial was ongoing (patients were implanted between 2016 and early 2017). RP is a progressive inherited retinal degeneration initially causing loss of peripheral vision that culminates, in the most severe cases, with near-total central and peripheral blindness. Prevalence is 0.025%[8], making it the most common inherited retinal degeneration or dystrophy. Unlike Prima, which is implanted at the sub-retinal layer and communicates with retinal bipolar cells, the epi-retinal Iris II aims to directly stimulate RGCs and its configuration has higher energy requirements (its electrode array requires power to be supplied through the use of permanent trans-scleral wires, resulting in a more time-consuming surgical procedure).

Six-month data released in autumn 2017 showed that, for the first five implanted patients, the device stopped operating correctly at approximately nine to 12 months post-implantation, or much earlier than originally anticipated. Pixium expected that the remaining implanted patients would eventually also reach the same outcome (premature lifetime exhaustion within a year of implantation), and suspended future Iris II implantations pending the identification of corrective improvements. It attributed the earlier than expected cessation of function to mechanical forces during product operation causing damage (through microfactures or breaks) to the trans-scleral wiring foil connecting extra-ocular housing to the intraocular electrode array fixed onto the patient's retina.

Pixium petitioned French regulatory agency since autumn 2017 to proceed with a re-implantation strategy to assess a proposed near-term corrective solution via surgery, and that also requires satisfactory long-term testing and validation. Following a recent internal review and also given the success in Prima's advancement into human studies and the assessment that Prima could deliver a superior risk/benefit balance (less invasive surgery, potentially higher VA), in an unmet market need (Dry-ARMD), and that it can eventually be developed for the RP indication, and given the time and

[8] Medscape. http://emedicine.medscape.com/article/1227488-overview#a6

costs that may be needed to develop and validate a longer-lasting Iris II device, Pixium decided to halt future Iris development and focus all resources instead on advancing Prima. Hence, we are removing all Iris II sales forecasts and R&D costs from our model.

The significant differences in design between the epi-retinal Iris II and sub-retinal Prima, most particularly the fact that Prima does not require trans-scleral wiring or cabling, lead us to believe that the mechanical stress-related operational disruptions that occurred with Iris II are unlikely to occur with Prima.

Competitive analysis

Pixium's products will need to compete with other implants on the market or in development.

Second Sight

Argus II uptake to date has been limited, as despite its presence on the market since 2011 in Europe (with US approval occurring in 2013), only 75 implants were sold worldwide in 2017 (vs 42 in 2016 and 75 in 2015). We believe the limited level of vision provided by the 60-electrode device (patients may still require mobility assistance) could help explain the limited uptake to date.

Retina Implant AG

Retina Implant is a private German company developing a sub-retinal implant for RP. Alpha IMS earned CE Mark in 2013 and a follow-on product, Alpha AMS, received CE Mark clearance in 2016. Alpha AMS intends to replace the functionality of degenerated photoreceptors by stimulating other retinal cells and its core chip measures 3.2 x 4 mm in size and is equipped with 1600 photodiodes (which convert the incident light into an electrical signal). Patients are not required to use a specialised external camera or goggles to communicate with the device (unlike Prima). However, unlike Prima, the Alpha AMS relies on external cabling to provide power to the device, and patients are required to have a conducting cable implanted through a section of the ocular globe, as well as a receptor implanted behind the ear in the cranial bone. These steps result in the need for two separate surgeries to implant the device, which is considerably more involved and time-consuming than what is required for Prima. Alpha AMS's more lengthy and comprehensive surgical requirement may restrain its commercialisation potential, in our view.

Retina Implant AG estimates that the technical characteristics of the Alpha AMS can provide a theoretical maximum VA of 7% (20/280) with a horizontal visual field of potentially up to 13°. The best VA achieved by a patient with the predecessor model (Alpha IMS) has been 3.7% (20/546).

While Alpha AMS has received CE Mark clearance, the firm's current commercialisation strategy is not fully clear. The company received approval from the French health authority under the Forfait Innovation (FI) programme, where the agency would cover the costs for the implant and treatment of a limited number of patients over a two-year period.

Nano Retina

Nano Retina is an Israel-based firm that is developing a miniature chip retinal implant, NR600, which is currently in preclinical development. The company claims that the product can be implanted using a minimally invasive surgical procedure in under one hour. Like Prima, the product would be self-powered, as its energy needs are met by photovoltaic elements generating operating voltage from infrared laser light delivered by the Nano Retina eyeglasses worn by the patient. The device candidate may support implantations at the epi-retinal and/or sub-retinal level, and we believe it is being designed to stimulate bipolar cells (similar to Prima).

iBionics

Based in Ottawa and founded in 2015, iBionics is designing an epi-retinal implant that stimulates the retina via diamond electrodes. The current iteration has 256 electrodes, with the possibility of increasing up to 1,024. The firm believes that a 1,024-pixel version could enable patients to recognise faces, read and navigate freely. Human trials are planned to start in 2020.

Other competing technologies

Alternate therapies (beyond electronic implants) are being developed to restore sight to patients with retinal diseases which, if successful, could compete with Iris Prima. These include:

- **Retinal transplantation** (ie transplantation of retinal cells or of immature retinal stem cells). This line of development is very premature and speculative with limited human data to date, but there have been reports of vision loss in some experimental treatments on ARMD patients.[9]
- **Neurological visual cortex stimulation.** Second Sight is developing a follow-on product (Orion I) that stimulates the visual cortex of the brain rather than the retina. By bypassing the optic nerve, Orion I could help patients with diseased optic nerves (eg glaucoma, optic neuropathy etc). The firm began an Orion I human feasibility study in January 2018 under the FDA's Expedited Access Pathway (EAP) programme and has guided that it may potentially begin a pivotal study in 2018. Neurosurgery is more invasive than retinal surgery, so we estimate that unless Orion I can provide better VA than Prima for retinal diseases, its potential use would likely be concentrated towards optic nerve diseases and thus may not directly compete with Prima.
- **Implantable telescope**. VisionCare Ophthalmic Technologies offers an FDA-approved implantable miniature telescope for ARMD, providing 2.2-2.7 times magnification, but it does not improve the ability of the damaged retina to resolve details.
- **Alternate sensory reproduction**. Wicab's BrainPort V100 projects an image recorded by a video camera mounted on a pair of sunglasses on to a tongue array containing 400 electrodes. This device can offer functionality in patients with damaged optic nerve transmission.

Financials

Pixium reported FY17 results on 8 February 2018, with €2.5m in revenue (primarily from subsidies and research tax credits, although €0.1m in commercial sales was booked from the sale of a single Iris II unit in Spain), a €12.7m in operating loss and €13.5m net loss (€1.02 per share). This compares to our expectations of operating and net losses of €12.5m and €13.3m, respectively. Operating cash flow was negative €11.5m, better than our forecast of negative €14.2m, as working capital needs were lower than anticipated.

Given the suspension of Iris II development, Pixium expects its operating cash burn rate in 2018 to decrease compared to 2017, even as it plans to pursue two separate Prima feasibility studies. We have lowered both our R&D and G&A spending forecasts (the latter to account for the cessation of Iris II commercialisation efforts). We now expect G&A costs of €3.5m and €3.6m in 2018 and 2019, respectively, versus our prior estimates of €3.6m and €8.2m, respectively. We have also reduced our 2018 and 2019 R&D cost forecasts to €7.2m and €15.0m, versus our prior estimates of €14.0m and €18.0m, respectively. We expect R&D costs to rise significantly y-o-y in 2019, given our view that costs for the EU Prima pivotal study will be significantly higher than the costs borne in 2018 for the feasibility trials. Consequently, we now forecast 2018 and 2019 cash burn rates (excluding net interest) of €7.3m and €17.3m, versus our prior estimates of €13.6m and €24.9m.

9 Kuriyan AE, Albini TA, Townsend JH, et al. N Engl J Med. 2017 Mar 16;376(11):1047-1053. doi:

Given the reduction in our burn rate estimates, we have lowered our projections for Pixium's financing needs to cover its expenditures. Whereas we previously anticipated the firm would need to raise €15m in 2018, €30m in 2019 and €40m in 2020, we have now lowered our funding requirement projections to €10m, €20m and €30m, respectively. With our Prima launch estimate now pushed to 2022, we now also anticipate the firm will need to raise €25m in 2021. We forecast that all this funding should enable the completion of registration-enabling Prima clinical studies in the EU to reach commercialisation in Europe, and positive cash flows resulting from EU sales should enable the completion of the US pivotal study. We continue to assume that Pixium will only start to become cash flow positive on a sustainable basis once Prima is launched (in 2022).

For illustrative purposes only, we have added our forecast funding requirements to long-term debt. However, it is possible that Pixium may be required to raise equity instead of debt, to meet its funding needs. Our financial and valuation models do not include the potential dilutive effects of future equity offerings

The company announced on 23 October 2017 that it has entered into an equity line of credit with Kepler Cheuvreux, which has provided a firm commitment to purchase 2m common shares of Pixium within two years. The shares will be issued based on the lowest of the daily volume-weighted average price of the two trading days preceding each issuance, minus a discount of up to 7.5%. 175,000 shares were issued in Q417 and subsequently, approximately 900,000 shares were issued through this facility, generating in our estimation, between €2.5-3.0m in funds for Pixium year-to-date.

Sensitivities

Development and regulatory risk. Much development risk remains with Prima as it has only recently begun to be tested on humans and longevity has not been proven. While there is favourable preclinical data, it is currently unknown whether Prima can provide superior central vision to epi-retinal implants and/or do so without additional safety risk. In addition, Prima is being advanced in patients with intact peripheral vision and it is uncertain how well the visual system in Prima-implanted patients will interpret natural intact peripheral vision with artificial central vision. Further, degradation of the inner retinal cells over time can reduce the VA offered by a retinal implant.

Commercial and competition risk. The visual improvements offered by Prima must be sufficient to persuade patients and insurers to cover the implant and be competitive vs alternative treatment options. Particular risk lies in the need for patients to properly undergo vision rehabilitation training to make full use of the Prima; if patients do not fully engage in this process, the level of vision improvement possible could be restrained, affecting the commercial value proposition and adoption level for the device.

Financing risk. Pixium's year-end 2017 gross cash of €10.5m, plus up to c €6m available through an equity facility (of which approximately 45% had been exercised since YE17), should support its runway through Q119. We assume Pixium will raise an additional €85m through year-end 2021 to sustain its operations and maintain its Prima commercial development strategy, as we do not expect Pixium to be cash flow positive until it launches Prima in 2022 in Europe. While our model accounts for these financings as long-term debt, the firm may need to issue equity instead and there is the risk that pricing is not favourable for current shareholders and leads to significant dilution.

Valuation

We continue to value Pixium using an rNPV approach, employing a 12.5% cost of capital. Given the firm's suspension of Iris II development, we have removed the Iris II opportunity from our valuation, and as stated earlier, we have also removed forecasts for Prima sales in RP from our valuation. Our valuation is now entirely based on the Prima opportunity in Dry-ARMD (although we may revisit the RP market if or when the company starts Prima human studies in RP patients).

We believe the successful activation of the Prima (with resulting light perception) in at least two patients is a noteworthy de-risking milestone and as such, we have raised the probability of success estimate for Prima-ARMD in our model to 15%, from 12.5% previously. We have also adjusted our forex assumptions for US sales, by using a spot rate of $1.25/€, vs $1.18/€ previously. After adjusting our launch timing and market share assumptions, our European pricing assumptions (as stated earlier) and rolling forward our estimates, we now obtain a pipeline rNPV (enterprise value) of €77.4m, down from €82.6m, previously. After including €1.4m in net cash at YE17 (€10.5m gross cash minus €1.5m in conditional advances and €7.6m in long-term debt), we obtain an equity valuation of €78.8m, or €5.44 per share (compared to €6.58 previously). The lower per-share valuation is also due to the increase in share count from our 24 October 2017 research note, due primarily to the exercise of the Kepler Cheuvreux equity line of credit (since the line of credit was announced in October 2017, 1.07m shares were exercised, with 900,000 exercised since YE17).

Exhibit 5: Pixium Vision rNPV assumptions

Product contributions (net of R&D and marketing costs)	Indication	Status	rNPV (€m)	rNPV/ share (€)	Probability of success	Launch year	Peak WW sales (€m)
Prima (net of R&D and marketing costs)	Age-related Macular degeneration	Human feasibility trials	159.7	11.01	15.00%	H122 (EU) and H223 (US)	1,013 in 2028
Corporate costs & expenses							
G&A expenses			(25.9)	(1.79)			
Net capex, NWC & taxes			(56.3)	(3.88)			
Total rNPV			77.4	5.34			
Net cash (debt) (2017)			1.4	0.10			
Total equity value			78.8	5.44			
FD shares outstanding (000) (Q118e)			14,500				

Source: Edison Investment Research

Exhibit 6: Financial summary

€(000)	2015	2016	2017	2018e	2019e	2020e
31-December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	3,296	2,516	2,535	2,500	2,500	0
Cost of Sales	0	(141)	(1,254)	0	0	0
General & Administrative	(2,680)	(2,953)	(4,526)	(3,500)	(3,588)	(4,677)
Research & Development	(15,169)	(10,869)	(8,486)	(7,200)	(15,000)	(16,000)
EBITDA	(14,552)	(11,448)	(11,730)	(8,200)	(16,088)	(20,677)
Depreciation	(1,144)	(1,051)	(936)	(1,043)	(1,751)	(1,570)
Amortization	0	0	0	0	0	0
Operating Profit (before exceptionals)	(15,697)	(12,499)	(12,666)	(9,243)	(17,839)	(22,248)
Exceptionals	0	0	0	0	0	0
Other	0	0	0	0	0	0
Operating Profit	(15,697)	(12,499)	(12,666)	(9,243)	(17,839)	(22,248)
Net Interest	52	58	(876)	(899)	(3,052)	(5,887)
Profit Before Tax (norm)	(15,644)	(12,441)	(13,542)	(10,143)	(20,891)	(28,134)
Profit Before Tax (FRS 3)	(15,644)	(12,441)	(13,542)	(10,143)	(20,891)	(28,134)
Tax	0	0	0	0	0	0
Profit After Tax and minority interests (norm)	(15,644)	(12,441)	(13,542)	(10,143)	(20,891)	(28,134)
Profit After Tax and minority interests (FRS 3)	(15,644)	(12,441)	(13,542)	(10,143)	(20,891)	(28,134)
Average Number of Shares Outstanding (m)	12.7	12.7	13.3	14.3	14.5	14.5
EPS - normalised (€)	(1.23)	(0.98)	(1.02)	(0.71)	(1.44)	(1.94)
EPS - normalised and fully diluted (€)	(1.23)	(0.98)	(1.02)	(0.71)	(1.44)	(1.94)
EPS - (IFRS) (€)	(1.23)	(0.98)	(1.02)	(0.71)	(1.44)	(1.94)
Dividend per share (€)	0.0	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET						
Fixed Assets	11,087	10,184	9,649	9,006	8,055	8,884
Intangible Assets	8,822	8,205	7,680	7,680	7,680	7,680
Tangible Assets	2,265	1,979	1,970	1,326	375	1,205
Current Assets	27,682	17,405	14,241	17,712	16,550	17,586
Short-term investments	0	0	0	0	0	0
Cash	24,354	14,244	10,532	14,911	13,749	14,785
Other	3,328	3,161	3,710	2,801	2,801	2,801
Current Liabilities	(3,498)	(2,836)	(2,752)	(2,752)	(1,530)	(1,530)
Creditors	(3,498)	(2,836)	(2,752)	(2,752)	(1,530)	(1,530)
Short term borrowings	0	0	0	0	0	0
Long Term Liabilities	(315)	(1,505)	(9,302)	(19,302)	(39,302)	(69,302)
Long term borrowings	(164)	(1,333)	(9,130)	(19,130)	(39,130)	(69,130)
Other long term liabilities	(151)	(172)	(172)	(172)	(172)	(172)
Net Assets	34,956	23,248	11,836	4,664	(16,227)	(44,362)
CASH FLOW						
Operating Cash Flow	(15,584)	(11,188)	(10,605)	(7,291)	(17,310)	(20,677)
Net Interest	52	58	(876)	(899)	(3,052)	(5,887)
Tax	0	0	0	0	0	0
Capex	(2,106)	(148)	(191)	(400)	(800)	(2,400)
Acquisitions/disposals	0	0	0	0	0	0
Financing	56	(0)	519	2,970	0	0
Net Cash Flow	(17,582)	(11,279)	(11,153)	(5,620)	(21,162)	(28,964)
Opening net debt/(cash)	(41,965)	(24,190)	(12,911)	(1,401)	4,219	25,381
HP finance leases initiated	0	0	0	0	0	0
Other	(193)	(0)	(357)	0	0	(0)
Closing net debt/(cash)	(24,190)	(12,911)	(1,401)	4,219	25,381	54,345

Source: Edison Investment Research, Pixium Vision accounts. Note: 2015 through 2017 revenues include tax credits and subsidies, which are forecast at approximately €2.5m per year in 2018 and 2019.

Contact details	Revenue by geography
74 rue du Faubourg Saint-Antoin 75012 Paris, France +33 1 76 21 47 30 www.pixium-vision.com	N/A

Management team

Chairman: Bernard Gilly	Chief executive officer; Khalid Ishaque
Bernard Gilly has over 20 years' experience in the financial and pharmaceutical sectors and as an entrepreneur. He was VP of R&D for five years at Pasteur Mérieux Connaught (now Sanofi Pasteur). He subsequently served as CEO of Transgene from 1992 to 2000. He later joined Sofinnova Partners in Paris (2000-05). In 2005, he founded and became the CEO of Fovea Pharmaceuticals. After Fovea was acquired by Sanofi in 2009, he became executive VP of the Ophthalmology division of Sanofi. He founded Pixium Vision in 2011.	Khalid Ishaque has over 20 years' experience in the medical technology sector. He joined Pixium Vision in 2014, having spent 17 years with Boston Scientific in various commercial and business development roles, and most recently as general manager of the International Neuromodulation division commercialising Spinal Cord and Deep Brain Stimulation systems for chronic pain and movement disorders. Before joining Boston Scientific in 1997, he worked for Becton Dickinson. He received a Master's degree in engineering from Cranfield Institute of Technology in the UK and his Master's in international economics and management from SDA Bocconi University in Italy.
Chief financial officer: Didier Laurens	**Chief technology officer : Guillaume Buc**
Prior to joining Pixium Vision, Didier served as director of IR, financing and treasury at Korian, where he also served as interim CFO. Previously, he was a financial analyst with Société Générale, covering various sectors including healthcare, where he was involved with numerous IPOs. He also served as marketing manager in the pharmaceutical industry. Didier holds a post-graduate degree in pharmacy and is a graduate of SFAF/CIIA.	Guillaume Buc has over 25 years' experience in technology development. Before joining Pixium Vision, Mr Buc held several management positions at GE Healthcare Europe. His latest role was CTO of the GE Healthcare interventional cardiology department. He received an engineering degree from the French Polytechnic Institute, in applied mathematics, and a degree from the Ecole Nationale Supérieure des Télécommunications / National Telecommunications School in Paris, in image processing and computer sciences.

Principal shareholders	(%)
Sofinnovia Venture	20.0
Abingworth	14.0
Bpifrance Investissement	10.7
Omnes Capital	9.7
Bpifrance Participations	7.0

Companies named in this report

Second Sight, Retina Implant AG, Nano Retina, iBionics

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