

# Quantum Genomics

The next generation of cardiac drugs

Initiation of coverage

Pharma & biotech

28 November 2016

**Price** €5.79

**Market cap** €49m

Net cash (€m) at 30 June 2016 13.22

Shares in issue 8.39m

Free float 61%

Code ALQGC

Primary exchange Alternext Paris

Secondary exchange N/A

## Share price performance



% 1m 3m 12m

Abs (9.1) (6.3) (37.9)

Rel (local) (9.2) (8.8) (33.8)

52-week high/low €8.76 €4.52

## Business description

Quantum Genomics is a biopharmaceutical company developing QGC001, a brain aminopeptidase A inhibitor for the treatment of hypertension and heart failure. Its mechanism is implicated in the 25% of patients resistant to treatment. In-human efficacy data are expected in June 2017.

## Next events

Hypertension Phase IIa data June 2017

Hypertension Phase IIb start H217

Heart failure Phase IIa data H118

## Analysts

Maxim Jacobs +1 646 653 7027

Nathaniel Calloway +1 646 653 7036

[healthcare@edisongroup.com](mailto:healthcare@edisongroup.com)

[Edison profile page](#)

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We are initiating coverage on Quantum Genomics, a biopharmaceutical company investigating brain aminopeptidase A inhibitors, a new class of drug, for the treatment of hypertension and heart failure with a completed and an ongoing Phase IIa study, respectively. This pathway has been implicated in patients with complicated hypertension including those who are resistant to other treatments (25%) and 52% of hypertensive African Americans. We initiate with a valuation of €172m.

Year end	Revenue (€m)	PBT* (€m)	EPS* (€)	DPS (€)	P/E (x)	Yield (%)
12/14	0.3	(2.5)	(0.46)	0.00	N/A	N/A
12/15	0.1	(4.5)	(0.55)	0.00	N/A	N/A
12/16e	0.1	(5.3)	(0.54)	0.00	N/A	N/A
12/17e	0.0	(5.3)	(0.52)	0.00	N/A	N/A

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

## Current drugs do not address the brain

The angiotensin pathway is one of the primary methods of modulating blood pressure and it is the target of some of the most successful anti-hypertensive drugs: angiotensin converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs). However, there is a parallel pathway in the brain responsible for the secretion of vasopressin and heart rate that is unaddressed by these classes of drug. The company completed a Phase IIa study (n=34) and has stated that results were positive, but the full data will be released in June 2017.

## 25% of patients currently underserved

There is a large population of individuals who are resistant to treatment with ARBs and ACE inhibitors. One class is so-called low renin primary hypertension, which is present in 25% of the 70 million hypertension patients in the US, but is endemic among hypertensive African Americans (52%). The brain angiotensin pathway is a central mechanism in this disorder, and currently the only treatment option for these patients is calcium channel blockers, which are associated with more side effects.

## Significant potential in heart failure

Hypertension is significantly comorbid with heart failure, and virtually every drug used to treat the former is also approved for the latter. Quantum Genomics has initiated a Phase IIa heart failure study (n=75). Despite a smaller market (six million US patients) it has a significantly higher price point and more research interest than hypertension, which may provide the leverage to secure a partnership.

## Valuation: €172m or €20.51/share

We value Quantum Genomics at €172m or €20.51/share based on a risk-adjusted NPV. We value the two programmes at €79m and €80m, although this represents higher revenue potential (\$2.1bn vs \$1.3bn peak sales) and higher development cost for hypertension. We forecast that the company will require €20m in financing before it can out-license the programmes in 2019 after completing Phase IIb studies.

## Investment summary

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### Company description: A new way to help the heart

Quantum Genomics is a development-stage pharmaceutical company advancing a compound (QGC001) for the treatment of hypertension and heart failure. QGC001 is an inhibitor of brain aminopeptidase A, which is important for the brain localised angiotensin pathway, which has been unaddressed by current therapeutics. This pathway is implicated in a large number of patients with complicated hypertension, and could potentially be combined with existing therapies. The company recently completed a Phase IIa study in hypertension, and has initiated a Phase IIa study in heart failure. Data should be released from the hypertension study in June 2017.

### Valuation: €172m or €20.51 per basic share

We value Quantum Genomics at €172m or €20.51/share based on a risk-adjusted NPV analysis of the company's lead programmes for hypertension and heart failure. We value the two programmes similarly, at €79m and €80m respectively, although hypertension has significantly higher peak sales estimates (\$2.1bn vs \$1.3bn) offset by increased development costs (\$206m vs \$111m). Both programmes are high risk (15% probability of success) on the basis of limited human efficacy data, but because of the high sales potential of these indications, signals of efficacy may contribute to significant valuation increases. We may further refine our valuation to reflect any future licensing deals. We expect the drug to launch in 2023, and have a runway through patent expiration in 2031.

### Financials: €20m needed to get to pivotal trials

Quantum Genomics ended H116 with €13.2m in cash and investments following a capital raise of €8.6m during the period. The net loss for the period was €2.8m, which we expect to decrease due to completion of the hypertension trial (€4.6m for the year). Due to the substantial costs associated with cardiac indications, we expect that the company will out-license QGC001 prior to pivotal trials before the end of 2019. However, we expect that the company will need an additional €20m in additional financing to complete the Phase II programmes for the molecule.

### Sensitivities: Limited human data and need to out-license

Although the company has completed a Phase IIa trial for QGC001, and although the company has stated the results were positive, the efficacy data from the trial has not been released, and will not be until mid-2017. Because of this, there is no in-human efficacy data for the compound, despite a robust backing in basic science and human safety profile. Therefore our success predictions are currently conservative. Additionally, regulatory authorities generally require cardiac outcome studies for hypertension and heart failure. In particular for hypertension, these studies can require exceptionally large numbers of patients, often over 10,000, because of the low underlying risk of complications. The numbers are lower for heart failure but often many thousands. Because these programmes are out of the scope that the company can accomplish alone, we assume that it will out-license the compound to a larger company to complete pivotal trials. This presents significant risk to the licensee because of the high development costs, and these factors could be part of the reason why many pharmaceutical companies are adverse to developing new compounds for these diseases. Therefore the data supporting QGC001 will have to be compelling to secure such a contract, and there is a risk that the company will not be able to secure a favourable contract, even in the event of demonstrated efficacy. This risk is partially mitigated by the comparably higher margins and development interest in the heart failure market compared to hypertension. Although the drug is differentiated from other classes and targets an underserved population, there may still be significant competition as there are hundreds of established brands.

## Heart trouble? It's all in your head

Quantum Genomics is a biopharmaceutical company based in Paris focused on the development of treatments for cardiac disorders. The company was founded in 2006 and has raised €32.1m to date from equity. It is developing a novel class of molecules targeting brain aminopeptidase A (BAPA) and one of these inhibitors (BAPAI) called QGC001 is currently in clinical trials for the treatment of hypertension (QGC001 programme, Phase IIa complete as of September 2016) and heart failure (QGC101, Phase IIa initiated June 2016). QGC001 is a prodrug of EC33, a compound used extensively in the laboratory setting to study BAPA. Additionally, the company is in clinical-enabling studies of this molecule in combination with an angiotensin converting enzyme (ACE) inhibitor for the treatment of hypertension (QGC011), and is in the early preclinical investigation of a next-generation BAPAI (QGC006). QGC001 is protected via a composition of matter patent until 2031.

### Exhibit 1: Quantum Genomics' pipeline

Program	Phase	Indication	Notes
QGC001	Phase IIa complete	Hypertension	Data June 2017, Phase IIb start H217
QGC011	Preclinical	Hypertension	Pharmacokinetic and toxicology studies
QGC006	Preclinical	Hypertension	Animal efficacy studies
QGC101	Phase IIa	Heart failure	Complete H217

Source: Quantum Genomics

## The role of angiotensin III

The renin-angiotensin pathway is a system of hormones that regulates blood pressure, and is the primary mechanism of regulating long-term changes in arterial pressure. The pathway involves a cascading series of sequential proteolytic modifications to angiotensin hormones spanning multiple organ systems. Renin is produced in the kidney in response to a decrease in blood perfusion, and this enzyme cleaves angiotensinogen produced in the liver from angiotensin I. Angiotensin I is subsequently cleaved by angiotensin converting enzyme (ACE) generated in the surface of the lungs into angiotensin II. Historically angiotensin II has been considered the primary effector of the system and is associated with vasoconstriction and aldosterone mediated sodium retention, resulting in an increase in arterial pressure. The increase in pressure consequently forms a feedback loop and inhibits the secretion of renin from the kidney. Significant development efforts into the area of hypertension have been focused on this pathway and there have been a large number of successful drugs developed as ACE inhibitors and angiotensin II receptor blockers (ARBs).

However, there exists a parallel renin-angiotensin pathway in the brain that is independent of the feedback loop with the kidneys.<sup>1</sup> This pathway also exerts significant control over arterial pressure, but unlike in the peripheral pathway, angiotensin II is not the terminal product. Angiotensin II is converted into angiotensin III in the brain by BAPA, and the molecule subsequently modulates a series of factors in the central nervous system that control blood pressure. First, angiotensin III is the primary mediator of vasopressin release from the pituitary, which leads to an increase in water retention in the kidneys and a rise in arterial pressure.<sup>2</sup> Secondly, angiotensin III is the primary mediator of the pressor response in the renin-angiotensin pathway.<sup>3</sup> The pressor response is the

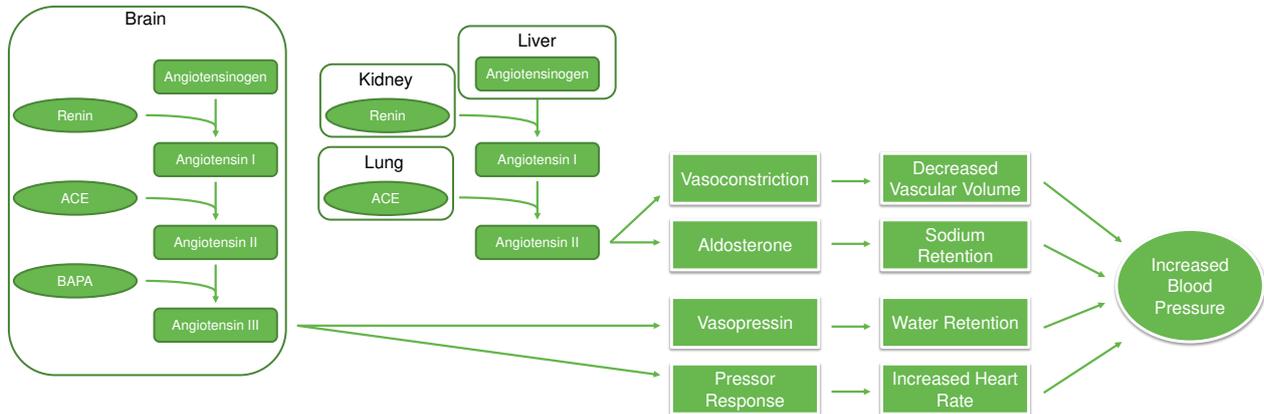
<sup>1</sup> Ganten D, et al. (1983) Angiotensin synthesis in the brain and increased turnover in hypertensive rats. *Science* 221, 869-871.

<sup>2</sup> Zini S, et al. (1996) Identification of metabolic pathways of brain angiotensin II and III using specific aminopeptidase inhibitors: Predominant role of angiotensin III in the control of vasopressin release. *Proc. Nat. Acad. Sci.* 93, 11968-11973.

<sup>3</sup> Reaux A, et al. (1999) Aminopeptidase A inhibitors as potential central antihypertensive agents. *Proc. Nat. Acad. Sci.* 96, 13415-13420.

increase in heart rate and blood pressure due to stress or excitement due to the activation of the sympathetic nervous system. Activation of the pressor response is important both for the pathology of hypertension as well as cardiac remodelling following myocardial infarction. Angiotensin II and III broadly share cross-reactivity between these different systems both *in vitro* and when exogenously administered, but under physiological conditions, the activity of angiotensin II is largely isolated to the periphery and angiotensin III to the brain.<sup>3</sup>

**Exhibit 2: Brain and peripheral renin-angiotensin pathway**



Source: Various, Edison Investment Research. Note: Angiotensin II and III share downstream cross-reactivity with effectors (not shown), and only the primary effectors based on site of generation are depicted.

## Hypertension

Quantum Genomics has multiple programmes investigating BAPA inhibitors (BAPAI) for the treatment of hypertension. The most advanced programme, QGC001, recently completed Phase IIa clinical trials in September 2016.

Hypertension is one of the most common medical conditions in the industrialised world, and is associated with increased risk of major cardiac events (heart attack, heart failure, aortic dissection, etc) and stroke. The age-adjusted prevalence in the US is 29% of adults,<sup>4</sup> and between 17% and 24% in Western Europe.<sup>5</sup> Diagnosis and treatment rates for the disease are high (83% and 76%, respectively), although the rate of control is low at only 52%.<sup>4</sup> A large cohort of patients appear to be resistant to multiple interventions and 12-15% of diagnosed hypertensive patients are unsuccessfully controlled following treatment with three or more drugs.<sup>6</sup>

The hypertension treatment market is exceptionally diverse, with approximately 200 approved formulations of different drugs and combinations, and over 400 brands. However, these drugs predominantly fall into one of five classes: ACE inhibitors, ARBs, calcium channel blockers, adrenoceptor agonists (including beta-blockers) and diuretics. Diuretics are generally the first line therapy, but may be combined with other drugs based on the severity of disease. Other first line treatments include restriction of dietary salt and exercise, as well as statins or aspirin to limit the associated cardiac risks. Beta-blockers are generally not recommended as first line therapy because they have the smallest impact on stroke risk and more severe adverse effects. Similarly, ARBs have been a subject of some controversy as they have been implicated in increased cancer risk and myocardial infarction. ACE inhibitors do not have these associated risks but are not

<sup>4</sup> CDC

<sup>5</sup> Kantar Health

<sup>6</sup> Pimenta E and Calhoun DA (2012) Resistant Hypertension: Incidence, Prevalence and Prognosis. *Circulation* 125, 1594-1496.

effective in certain patients (see below). Calcium channel blockers are effective at reducing cardiac risk in otherwise hard to treat populations such as those with low renin (see below). However, because the side effects of channel blockers are more severe (light-headedness, nausea, diarrhoea, swelling of the extremities), they are generally not prescribed to the larger population. Because of the large number of available products, the cost per patient is relatively low for this indication at approximately \$1,000 a year for a branded drug. Based on the data available from Symphony Health, we estimate a US market for these classes of drugs in excess of \$34bn in 2015, including generics, although many of these prescriptions may be for related indications such as heart failure and coronary artery disease. Sales of individual drugs can be significant, despite the competitive nature of the market. For instance Diovan has peak sales of \$6bn in 2010, and the brands Aceon, Micardis, Avapro, Benicar and Cozaar all achieved over \$1bn in sales.

Exhibit 3: Hypertension treatment drug classes		
Drug class	Brand examples	Notes
ACE inhibitor	Aceon, Tritace, Vasotec, Zestril, Prinivil	Prevents angiotensin II synthesis.
ARB	Micardis, Avapro, Benicar, Diovan, Cozaar	Prevents downstream effects of angiotensins. May increase risk of cancer and myocardial infarction.
Calcium channel blocker	Norvasc, Adalat, Plendil, Sycor, Zandip	Relaxes vascular smooth muscle. Only effect treatment for LRPH.
Adrenoceptor agonist	Seloken, Concor, Lobivon, Bystolic, Coreg	Inhibits sympathetic nervous system. Not recommended as a first line treatment because it does not reduce stroke risk.
Diuretic	Natrilix, Verospiron, Luprac	Reduces fluid volume. First line treatment.

Source: Evaluate Pharma

Very little research is devoted to developing novel therapies for hypertension. The vast majority of development programmes are for combinations of existing drugs, usually combining multiple drug classes into a single pill. A significant reason behind this is that the development costs for anti-hypertensive drugs, and for cardiac indications in general, are exceptionally high. Although trials to establish antihypertensive claims can be of a relatively normal size (n=400-600), regulatory bodies typically require outcome trials to support claims of a reduction in myocardial infarction or other major events. For instance, Zestril (Lisinopril, AstraZeneca) underwent a 438-person trial to support anti-hypertensive claims, but a 19,394-person trial to support a reduction in myocardial infarction. Because of these limitations, the vast majority of research into antihypertensive drugs has been performed by large pharmaceutical companies. Because of this, we expect Quantum Genomics will seek a partner to advance development of QGC001 past Phase II, pending positive data.

## Low renin primary hypertension

There are multiple varieties of hypertension with underlying genetic origins. One such disorder is called low renin primary hypertension (LRPH, also known as low renin essential hypertension) because it is characterised by high blood pressure despite lower than average levels of circulating renin. The disorder is additionally characterised by high concentrations of vasopressin and increased sensitivity to sodium, which is consistent with the hyperactivity of the brain renin-angiotensin system and consequent downregulation of the peripheral system.<sup>7</sup> These patients are generally resistant to ACE inhibitors, ARBs and beta-blockers, and the only treatment option is calcium channel blockers.<sup>8</sup> Quantum Genomics has identified patients with LRPH as a potential market for BAPAI because of the unique mechanism and the relative lack of options for these patients.

Although it exists on a spectrum, approximately 25% of hypertensive patients are characterised as having low renin.<sup>8</sup> However, many ethnic groups have dramatically higher prevalence of the

<sup>7</sup> Basso N, et al. (1981) Renin-like activity in the rat brain during the development of DOC-salt hypertension. *Hypertension* 3, 11-14.

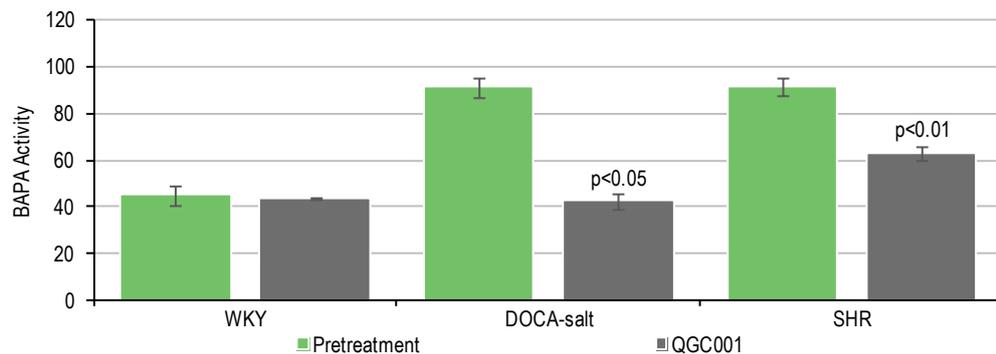
<sup>8</sup> Bühler FR, et al. (1984) Renin profiling to select antihypertensive baseline drugs. Renin inhibitors for high-renin and calcium entry blockers for low-renin patients. *Am. J. Med.* 77, 36.

disorder. For instance, the prevalence of LRPH among hypertensive patients of African origin is approximately twice (52%) that of the general population in the US.<sup>9</sup> This is in addition to higher background rates of hypertension (44% of adults) among African Americans.<sup>4</sup> Even among people with normal blood pressure, renin activity in African Americans is approximately half of that seen in Caucasians.

## Basis of QGC001 for hypertension

The most detailed data we have on the activity of QGC001 for the treatment of hypertension is from preclinical animal studies. These studies examined the activity of the compound in normotensive rats (genotype Wistar Kyoto), rats induced into a low renin hypertensive state through the administration of deoxycorticosterone acetate and saline, so called DOCA-salt rats, and spontaneously hypertensive rats (SHR), which have normal renin levels. The first goal of these studies was to establish that the compound was orally active in these models, and effectively prevented the generation of angiotensin III by BAPA. The BAPA activity in the brains of the animals was measured both before and after treatment with the drug (Exhibit 4). First, it was found that the activity of this enzyme was approximately twice that of control rats before any treatment for both the DOCA-salt and SHR animals, which suggests a role in their pathology. When QGC001 was administered, the level of BAPA activity in the DOCA-salt rats dropped by approximately 47% to the level of the control rats. This is consistent with the hypothesis BAPA is a primary mediator of hypertension with low renin. By comparison, BAPA activity in the SHR cohort was reduced by 31%, and there was no effect in the control animals.

**Exhibit 4: Brain APA activity in DOCA-salt and spontaneously hypertensive rats**



Source: Bodineau et al.,<sup>10</sup> Marc et al.<sup>11</sup> Notes: WKY=Wistar Kyoto rats (control), SHR=spontaneously hypertensive rat, activity given in nmol β-naphthylamide generation per hour per milligram of protein. Error bars = SEM.

A similar trend was seen when examining the mean blood pressure of the animals: 15mg/kg QGC001 had a more pronounced effect in the DOCA-salt rats (18% reduction in mean blood pressure) than the SHRs (11% reduction) and there was no effect in the control (Exhibit 5). The effect of higher doses was also reported in the SHR study. At a higher dose (50mg/kg), the reduction in blood pressure was similar between QGC001 (173.2 to 150.3 mmHg, p<0.001) and 3mg/kg of the ACE inhibitor Vasotec (enalapril, Valeant, 179.6 to 153.1 mmHg, p<0.001), and the effect of the two drugs was additive (p<0.01). Although the SHR animals do not model the low renin human population, the additive effect of these drugs poses the possibility that QGC001 can be used

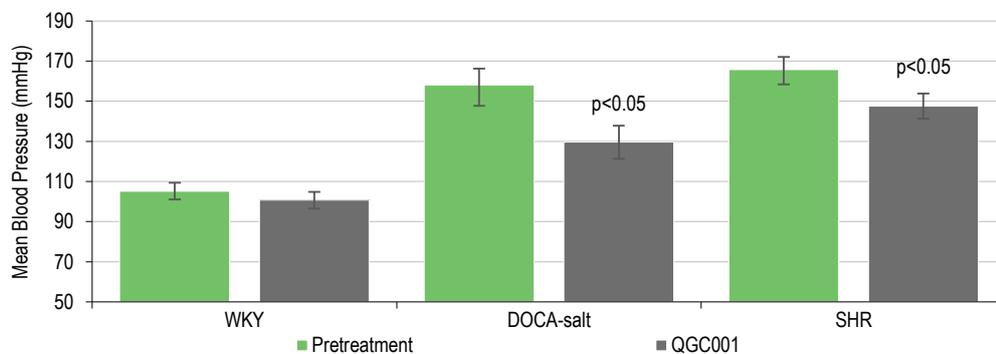
<sup>9</sup> Sagnella (2001) Why is plasma renin activity lower in populations of African origin? *J. Hum. Hypertension* 15, 17-25.

<sup>10</sup> Bodineau L, et al (2008) Orally Active Aminopeptidase A Inhibitors Reduce Blood Pressure. *Hypertension* 51, 1318-1325.

<sup>11</sup> Marc Y, et al. (2012) Central Antihypertensive Effects of Orally Active Aminopeptidase A Inhibitors in Spontaneously Hypertensive Rats. *Hypertension* 60, 411-418.

in a combination to treat a broader population of patients underserved by existing treatment regimens. The company is in preclinical development of a combination of QGC001 with either an ACE inhibitor or ARB (the QGC011 programme) with these aims.

**Exhibit 5: Mean blood pressure in DOCA-salt and spontaneously hypertensive rats following 15mg/kg QGC001**



Source: Bodineau et al.,<sup>10</sup> Marc et al.<sup>11</sup> Notes: WKY=Wistar Kyoto rats (control), SHR=spontaneously hypertensive rat. Error bars = SEM.

The company has completed two clinical studies of QGC001 in human subjects. The first was a Phase I dose-ranging study investigating the drug in healthy patients.<sup>12</sup> The 56-person study investigated doses of the drug up to 1,250mg. Six mild to moderate adverse events were reported in the trial, and the only potential treatment related event was a single case of asymptomatic orthostatic hypotension. Across the study group, the drug did not affect blood pressure or heart rate, consistent with the results in normotensive animals.

The company completed a 34-person Phase IIa study of QGC001 investigating efficacy in the general hypertension population. The randomised, double-blind trial employed a crossover design with patients receiving either QGC001 or placebo for four-week periods. The efficacy endpoints of the trial were multiple blood pressure measurements: a 24 hour ambulatory measurement, a measurement at home and a measurement in the doctor's office. In September 2016, it reported the following:

"The data show positive signals on several endpoints, in particular on the primary endpoint of the study, specifically a drop in daytime systolic blood pressure measured as ambulatory pressure in hypertensive patients, treated with QGC001 as compared with placebo. This positive result is confirmed by an in-depth multivariate analysis."

However, the company is withholding detailed results until they can be presented at the European Society of Hypertension conference in June 2017. The full results have been presented to the FDA, which has provided guidance on the plan for a Phase IIb study. The new trial will examine the efficacy of the drug in a "target population" we expect to be low renin patients, and it will initiate in H217.

## Heart failure

Quantum Genomics is also investigating the QGC001 compound for the treatment of heart failure in the QGC101 programme. Heart failure is a clinical diagnosis representing a cluster of disorders in

<sup>12</sup> Balavoine F (2014) Randomised, double-blind, placebo-controlled, dose-escalating phase I study of QGC001, a centrally acting aminopeptidase a inhibitor prodrug. *Clin. Pharmacokinetics*, 53, 385-395.

which the heart has a reduced ability to pump blood. There are an estimated 5.8m cases of heart failure in the US and 550k new cases diagnosed per year.<sup>13</sup>

Drugs of the same classes used to treat hypertension are also used for heart failure, because a reduction in blood pressure reduces strain on the heart and prevents the associated hypertrophy and other disorders that can lead to reduced function. Moreover, drugs such as beta-blockers can directly affect the cardiac workload by modulating the activity of the sympathetic nervous system. However, unlike for hypertension, there is greater research into new treatments for heart failure. These new therapies include cell therapies to encourage the development of healthy cardiac tissue, as well as factors to improve cardiac muscle function and heart output. Drugs specifically for this indication tend to command higher prices than for hypertension, in the range of \$4,000-5,000 per year. The total market size for heart failure is hard to estimate separately from the overlapping hypertension market, as they are largely shared by the same classes of drug, totalling over \$34bn in the US.

#### Exhibit 6: Selected heart failure development programmes

Drug	Sponsor	Phase	Description
Vericiguat	Merck/Bayer	Phase III	Guanylate cyclase activator
MPC-150-IM	Mesoblast	Phase III	Mesenchymal stem cell
GSK2798745	GlaxoSmithKline	Phase II	Transient receptor potential vanilloid-4 (TRPV4) antagonist
Omecamtiv mecarbil	Amgen	Phase II	Cardiac myosin activator
Elamipretide	Stealth BioTherapeutics	Phase II	Mitochondria targeted therapy
PB1046	PhaseBio Pharmaceuticals	Phase II	Vasoactive intestinal peptide (VIP) receptor 2 (VPAC2) agonist
Stemedyne-MSD	Stemedica Cell Technologies	Phase II	Cardiac stem cell therapy
Cimaglermin Alfa	Acorda Therapeutics	Phase I	Glial growth factor 2
CAP-1002	Capricor Therapeutics	Phase I	Cardiovascular cell therapy agent

Source: Evaluate Pharma

Development for heart failure is more efficient than for hypertension because the rate of cardiac events associated with the disorder is significantly higher and shorter trials with fewer patients are needed. The ongoing Phase III clinical trial for Vericiguat (Merck/Bayer) has a targeted enrolment of 4,872, whereas the Phase III trial of MPC-150-IM (Mesoblast) recently reduced its target enrolment from 1,165 to 600 due to difficulty recruiting.

## Preclinical studies

The compound in QGC001 is attractive as an agent to treat heart failure because the brain renin-angiotensin pathway is implicated in activating the sympathetic nervous system in addition to its other roles in regulating blood pressure. It therefore has the potential to reduce activation of cardiac muscle similar to beta-blockers without the associated side effects. The company is advancing the compound in a separate clinical programme (QGC101) for the treatment of patients with heart failure.

Quantum Genomics published an investigation of the drug for the indication in rats in 2013.<sup>14</sup> Following an induced myocardial infarction (MI), rats were treated with either vehicle, 0.3mg/day QGC001, or 0.25mg/day of the ARB Cozaar (losartan, Merck). An important preliminary finding of the study was that the brain angiotensin pathway was significantly activated following MI in both the vehicle and Cozaar arms. The rats treated with QGC001 had BAPA activity levels similar to those non-MI rats. At the four-week point, QGC001 had improved blood pressure in these animals to the level of non-MI rats, significantly better than losartan ( $p < 0.05$ ). Improvement in heart rate and sympathetic nerve activity was similar between the QGC001 and Cozaar arms. When the animals were examined using echocardiography, the ejection fraction had recovered approximately 25-30%,

<sup>13</sup> Roger VL (2013) Epidemiology of Heart Failure. *Circ. Res.* 113, 646-659.

<sup>14</sup> Huang BS, et al. (2013) Inhibition of brain angiotensin III attenuates sympathetic hyperactivity and cardiac dysfunction in rats post-myocardial infarction. *Card. Res.* 97, 424-431.

significantly greater than vehicle ( $p < 0.05$ ) and Cozaar ( $p < 0.05$ ). QGC001 appeared to improve the pumping efficiency of the heart by improving both maximum and minimum pressure differentials over vehicle ( $p < 0.001$ ) and Cozaar ( $p < 0.05$ ), which had no effect.

The company initiated a Phase IIa clinical study of QGC001 for heart failure patients in June 2016. The 75-person trial is designed to be conducted over 10 sites in Europe, and is expected to end in Q417.

## Sensitivities

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Quantum Genomics faces a series of development and commercial challenges, many of which are common to companies in the early stages of development, and some that are unique to companies engaged in cardiac research. Although the biochemical pathway being investigated is well understood and we have a high degree of confidence that modulating this pathway could be impactful for hypertension and heart failure, the efficacy data supporting the activity of QGC001 is currently limited to animal models. A trial in humans has been completed, but unfortunately results will not be released until mid-2017. We therefore do not have a clear picture of the degree of efficacy in humans. However, the decision by the company to advance the hypertension programme in light of FDA feedback is encouraging.

We do not expect Quantum Genomics to be able to advance the clinical programme for either hypertension or heart failure beyond Phase II without a partnership. As mentioned above, pivotal trials for cardiac indications typically require many thousands of enrollees, hypertension in particular requiring tens of thousands. We believe that this is beyond the scope of what the company can achieve alone as the capital expenditure is outside of what it could reasonably raise. Moreover, the large pharmaceutical companies that could potentially execute such a trial have been adverse to the development of new compounds for hypertension in recent years. However, the unmet medical need in low renin patients may allow for premium pricing and an additional development incentive. There has also been more interest in the development of heart failure treatments, so this might mitigate some of the partnering risk. However, the company may not be able to advance the clinical programmes, even if effective, if it cannot attract the interest of another much larger pharmaceutical company. The partnership of the compound should mitigate the future funding requirements for the company, but we expect that it will need approximately €20m in additional financing before a potential discussion can occur, which we conservatively model in 2019.

The compound will also face a series of commercial risks in the event of approval, and these future risks may weigh on partnering discussions. First, there are a large number of approved drugs for the treatment hypertension and heart failure, measuring in the hundreds, with most being available as a generic. In particular, drugs approved for hypertension have a very low price point as the result of this competition, at approximately \$1,000 per year for a branded drug. The drug could potentially command a price four or five times as high for heart failure, although this market is still very competitive by comparison to non-cardiac drugs, and significant marketing efforts may be required.

## Valuation

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We arrive at an initial valuation of €172m or €20.51 per basic share based on a risk-adjusted NPV analysis. We currently include only the hypertension and heart failure programmes in our model, as these are the only programmes in the clinic. Although we fully expect that the company will out-license the compound for development beyond Phase II for royalties and milestones, for the purposes of our valuation, we model the entire development pathway and costs of selling to get an accurate picture of the current value of these assets. The future value of the company may be

significantly affected by the licensing or sale of these assets and the impact of goodwill or leverage over the company, although we are currently not speculating as to these effects. More detailed knowledge of the risk profile of the drug may allow us to better assess future deal terms.

For both programmes we assume a 2023 launch year based on the timing of their clinical programmes. Additionally we assume 30% lower prices in Europe and 30% discount to payers from gross sales.

Our current valuation for the hypertension programme arrives at a net value of €79m. We model the target market as the 12.8% of hypertension patients who are poorly controlled after three or more drugs, and assume 10% penetration in this market. We expect the costs of selling to be high (\$10m fixed costs and 20% variable costs) due to the need to target primary care physicians and potentially engage in direct to consumer advertising. We assume a US WAC of approximately \$1,500 per year, which is based on a 20% premium to the price of Edarbi (azilsartan medoxomil, Takeda, AWP of \$3.56 per day in 2013), adjusted for a 2% yearly price growth to the 2023 launch year. R&D costs for the programme are expected to be exceptional. We model the cost per patient at \$20k, and 300 patients for the upcoming Phase IIb programme, and 10,000 patients in the pivotal programme. Our probability of success is 15% based on the limited efficacy data available at this point.

We also arrive at a valuation for the heart failure programme of €80m. We assume a similar market segment of those patients who are poorly controlled by ACE inhibitors, ARBs, etc, limited to the smaller total heart failure market. However, we assume a higher peak penetration of 15% due to the severity of the disease and the increased medical need. Our costs of selling are lower (\$5m fixed and 10% variable) than for hypertension as we expect the majority of prescriptions to be made from the smaller cardiologist prescriber base. We assume a higher average US WAC for this formulation of approximately \$6,400 at launch, based on the price of Entresto (sacubitril/valsartan, Novartis, \$15 a day AWP in 2016). Note that the treatment cost for this indication is higher than for hypertension and this price may be affected in the future if the drug is approved for both indications. In this case the variable pricing will be dependent on the quantity of drug needed for the treatment of heart failure in comparison to hypertension, which we have little insight into at this time. For clinical trials, we model higher per patient costs (\$50k) for heart failure due to the higher risk of complication. We model the ongoing Phase IIa with a peak enrolment of 75. We expect a Phase IIb starting in 2018 with 150 patients and at least 2,000 patients for pivotal trials in 2019. We model a 15% probability of success for this programme as well, based on the similar lack of in-human efficacy data.

We expect to adjust our valuation with the release of the hypertension Phase IIa data from in June 2017. Additional factors that could affect our valuation are the advancement of the QGC011 or QGC006 programmes, which we currently do not include, or any partnering developments.

#### Exhibit 7: Quantum Genomics valuation

Product	Main indication	Local	Status	Prob. of success	Launch year	Peak sales (\$m)	Patent protection	rNPV (€m)
QGC001	Hypertension	US	Phase IIa complete	15%	2023	\$1,110	2031	€99.12
QGC001	Hypertension	Europe	Phase IIa complete	15%	2023	\$959	2031	€84.08
QGC001	Development costs							(€104.55)
QGC101	Heart failure	US	Phase IIa	15%	2023	\$574	2031	€63.08
QGC101	Heart failure	Europe	Phase IIa	15%	2023	\$687	2031	€74.85
QGC101	Development costs							(€57.70)
Total								€158.87
Cash and cash equivalents (H116) (€m)								€13.22
Total firm value (€m)								€172.09
Total shares (m)								8.39
Value per basic share (€)								€20.51

Source: Edison Investment Research, Quantum Genomics reports

## Financials

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Quantum Genomics reported a loss of €2.8m for H116, which is an increase over previous periods (€1.8m for H115 and €2.0m for H215). This is largely attributable to the initiation of the heart failure programme, but we expect this value to be lower going forward (€4.6m for the year) due to the completion of the hypertension Phase IIa trial. We expect spending to increase with the advancement of the two programmes into Phase IIb trials, in 2018 and 2019, but subsequent partnering of the compounds should substantially limit further spending on these programmes. The company ended H116 with €13.2m in cash and investments following a €8.6m financing during the period. We expect that this will be sufficient to complete the heart failure Phase IIa trial, but that the company will need additional financing to progress the two programmes. We currently predict additional funding of €20m will be needed (predicted in 2018) before the programs are complete in 2019, but further financing will likely not be necessary if the company can secure a deal to develop the asset further.

**Exhibit 8: Financial summary**

€000s	2014	2015	2016e	2017e
Year end 31 December	IFRS	IFRS	IFRS	IFRS
<b>PROFIT &amp; LOSS</b>				
Revenue	324	144	138	0
Cost of Sales	0	(0)	0	0
Gross Profit	324	144	138	0
EBITDA	(2,418)	(4,310)	(5,126)	(5,138)
Operating Profit (before GW and except.)	(2,418)	(4,310)	(5,126)	(5,138)
Intangible Amortisation	0	0	0	0
Other	0	0	0	0
Exceptionals	0	0	0	0
Operating Profit	(2,418)	(4,310)	(5,126)	(5,138)
Net Interest	(20)	(222)	(162)	(162)
Other	(105)	54	54	0
Profit Before Tax (norm)	(2,537)	(4,503)	(5,288)	(5,300)
Profit Before Tax (FRS 3)	(2,542)	(4,479)	(5,234)	(5,300)
Tax	335	714	680	689
Deferred tax	0	0	0	0
Profit After Tax (norm)	(2,202)	(3,789)	(4,608)	(4,611)
Profit After Tax (FRS 3)	(2,207)	(3,765)	(4,554)	(4,611)
Average Number of Shares Outstanding (m)	4.8	6.9	8.5	8.9
EPS - normalised (€)	(0.46)	(0.55)	(0.54)	(0.52)
EPS - FRS 3 (€)	(0.46)	(0.54)	(0.53)	(0.52)
Dividend per share (€)	0.0	0.0	0.0	0.0
<b>BALANCE SHEET</b>				
Fixed Assets	623	520	459	479
Intangible Assets	66	108	104	104
Tangible Assets	32	54	11	31
Other	525	358	344	344
Current Assets	4,129	10,020	13,584	8,953
Stocks	0	14	125	125
Debtors	811	1,354	2,001	2,001
Cash	3,318	8,652	11,458	6,827
Other	0	0	0	0
Current Liabilities	(4,035)	(728)	(788)	(788)
Creditors	(728)	(728)	(788)	(788)
Short term borrowings	(3,308)	(1)	(1)	(1)
Long Term Liabilities	(847)	(1,790)	(2,028)	(2,028)
Long term borrowings	(847)	(1,790)	(2,028)	(2,028)
Other long term liabilities	0	0	0	0
Net Assets	(130)	8,022	11,227	6,615
<b>CASH FLOW</b>				
Operating Cash Flow	(2,791)	(3,142)	(4,963)	(4,609)
Net Interest	0	0	0	0
Tax	0	0	0	0
Capex	(304)	(72)	(22)	(22)
Acquisitions/disposals	0	0	0	0
Financing	3,699	12,150	7,758	0
Dividends	0	0	0	0
Other	116	(296)	33	0
Net Cash Flow	719	8,640	2,806	(4,631)
Opening net debt/(cash)	118	837	(6,861)	(9,429)
HP finance leases initiated	0	0	0	0
Exchange rate movements	0	0	0	0
Other	(1,438)	(942)	(238)	0
Closing net debt/(cash)	837	(6,861)	(9,429)	(4,798)

Source: Edison Investment Research, Quantum Genomics reports

<b>Contact details</b> Tour Maine Montparnasse 33 Av du Maine Paris, 75015 France +30 0 1 60 13 76 84 www.quantum-genomics.com	<b>Revenue by geography</b> N/A
<b>Management team</b> <b>President and CEO: Lionel Ségard</b> Mr Ségard is the former CEO of Inserm-Transfert, a subsidiary of INSERM (the French National Institute for Health and Medical Research), founder and former president of Inserm Transfert Initiative (a seed fund dedicated to young innovative healthcare companies) and founder of the Strategic Council for Innovation (secretary general from 2003 to 2005). He is a biochemist by training (University of South Paris – Orsay).	<b>CFO: Marc Karako</b> Mr Karako was previously executive vice president & chief financial officer of Carlson Wagonlit Travel, chief financial and legal officer of Vallourec, and vice president of finance at Thomson Multimedia. He previously worked for 10 years at IBM in various financial management positions and holds a master's of engineering (Ecole des Ponts ParisTech) and an MBA from the University of Chicago.
<b>CMO: Olivier Madonna</b> Dr Madonna has an in depth knowledge of international R&D processes within pharmaceutical, biotech and medical device industries, with previous experience as head of cardiovascular medical departments with MSD and J&J. He holds an MD and is a certified cardiologist, nephrologist and specialist in internal medicine.	<b>COO: Jean-Philippe Milon</b> Mr Milon previously held several management positions at Bayer HealthCare, including being a member of the Worldwide Executive Committee as head of WW Business Development, Licensing, Mergers & Acquisitions. Additionally he previously was head of the cardiovascular business at Sandoz. He holds more than 25 years of experience in healthcare mainly in the pharmaceutical industry.
<b>Principal shareholders</b>	<b>(%)</b>
Alix Asset Management	16.5%
Tethys	11.9%
Grand Allied	8.73%
Delore & Associates SAS	3.34%
Norges Bank Investment Management	1.44%
<b>Companies named in this report</b> AstraZeneca (AZN), Valeant (VRX), Merck (MRK), Bayer (ETR:BAYN), Mesoblast (MESO), Takeda (TYO:4502), Novartis (NVS)	

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