EDISON

Atossa Genetics

Pipeline advancement

Multiple opportunities to address breast health

Pharma & biotech

Atossa Genetics's endoxifen programs are advancing in their respective breast health programs. The firm recently reported positive safety data from its Phase I study on topical endoxifen in men, and it completed enrolment for its Phase II endoxifen study in women with elevated mammographic breast density (MBD). It is also advancing an oral endoxifen formulation in women refractory to tamoxifen, and is applying its intraductal microcatheter (IDMC) with cancer drug fulvestrant. Our rNPV-derived equity valuation is $23.9m, or $3.66 per share.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/16	0.0	(7.2)	(29.52)	0.0	N/A	N/A
12/17	0.0	(7.2)	(10.01)	0.0	N/A	N/A
12/18e	0.0	(12.9)	(4.31)	0.0	N/A	N/A
12/19e	0.0	(11.7)	(1.88)	0.0	N/A	N/A

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

Topical endoxifen targets MBD, gynecomastia

Oral tamoxifen, a selective estrogen receptor modulation (SERM) drug, reduces both MBD and the risk of cancer recurrence in women with breast cancer, but its adverse effects (AE) have limited its use. Endoxifen is a tamoxifen metabolite that is responsible for much of the oral drug's SERM action. Atossa believes that topical endoxifen can exert SERM effects to breast tissue and reduce MBD, with fewer significant AE. It also believes that topical endoxifen can safely reduce gynecomastia (male breast enlargement). A Phase II MBD study is underway, although preliminary suggestions of skin rashes and irritation have been reported. A Phase II gynecomastia study in male prostate cancer patients is planned for 2019.

Oral endoxifen for women refractory to oral tamoxifen

About 20% of the 300,000 US women currently taking tamoxifen (largely to prevent recurrence of breast cancer) do not achieve sufficient concentrations of endoxifen and may have increased risk of cancer recurrence. Atossa believes that oral endoxifen can reduce recurrence risk in these patients and it plans to start a Phase II study in 2019.

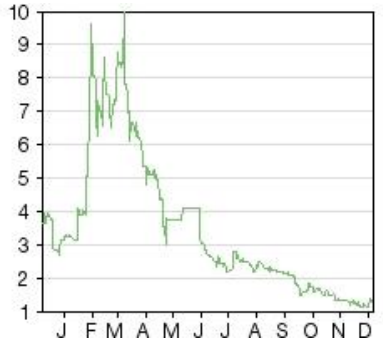
Valuation: Equity valuation of $23.9m

Atossa had $13.0m net cash at 30 September 2018. We expect its funds on hand to last into early 2020 and that it will raise $10m in 2019. For modelling purposes, we assign these financings to long-term debt. Our rNPV valuation includes the prospect of the firm's topical and oral endoxifen programs for women, its IDMC-delivered fulvestrant program and now its gynecomastia program as well. We now obtain a lower rNPV valuation of $10.9m (vs $24.4m, previously), largely due to a lower success probability (4% vs 5%, previously) for the MBD program. After including Q318 net cash ($13.0m), we obtain an equity valuation of $23.9m, or $3.66 per fully diluted (FD) share (which assumes full conversion of 3,517 outstanding Series B convertible preferred shares into 1.0m common shares).

7 December 2018

Price	**US$1.30**
Market cap	**US$7m**
Net cash ($m) at Q318	13.0
Shares in issue	5.1m
Free float	99.5%
Code	ATOS
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	(3.0)	(37.5)	(64.6)
Rel (local)	(0.8)	(33.3)	(65.5)
52-week high/low	US$10.0		US$1.1

Business description

Based in Seattle, WA, Atossa Genetics is a clinical-stage pharmaceutical firm developing therapeutics and delivery methods to treat breast cancer and other breast conditions. Intraductal microcatheter-delivered fulvestrant and endoxifen are both in clinical stages of development.

Next events

Q318 results	November 2018
Results from Phase II MBD topical endoxifen trial	Q219

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Investment summary

Company description: Targeted therapies in breast health

Atossa Genetics initially developed medical devices and laboratory services before transitioning to drug development in recent years. It is developing endoxifen, a tamoxifen metabolite intended to provide selective ER antagonism. A topical formulation is being advanced for the treatment of MBD and gynecomastia, and an oral formulation is being developed for breast cancer prevention. A Phase II study in MBD is underway, and Phase II studies for gynecomastia and cancer prevention in women refractory to tamoxifen are expected to start in 2019. Reports of skin irritations in the ongoing Phase II MBD trial raise concerns on product safety and may delay its development. Atossa also has rights to an IDMC device intended to selectively introduce drugs to breast ducts, potentially improving targeting for chimeric antigen receptor (CAR) T-cell and chemotherapy uses. Atossa is performing a Phase II study combining the IDMC with established cancer drug fulvestrant.

Exhibit 1: Atossa Genetics current pipeline

Product	Status
Topical endoxifen	
Phase II female study to determine effects on MBD	Enrolment complete; Study ongoing
Phase II male study to treat gynecomastia in mean being treated for prostate cancer	CRO to be retained in Q418
Oral endoxifen (in females)	
Phase II study to determine if tumor activity reduced in early stage breast cancer	Recruitment underway in Australia
Phase II study in patients who are refractory to tamoxifen	CRO to be retained in Q418
Intraductal delivery	
Phase II study of fulvestrant in cancer patients prior to surgery	Enrolment underway
Immunoncology (CAR-T research)	Preclinical

Source: Company reports. Note: CRO = contract research organization.

Valuation: Equity value of $23.9m

Our rNPV valuation applies a 12.5% discount rate and includes the prospects of the firm's topical endoxifen programs in MBD and gynecomastia, and its oral endoxifen and its IDMC-delivered fulvestrant programs. We apply a 20% probability of success estimate for oral endoxifen, a 4% probability for topical endoxifen in MBD (vs 5% previously), a 4% probability in gynecomastia, and a 10% probability for the IDMC-fulvestrant program. After also raising our G&A cost estimates, we now obtain an rNPV valuation of $10.9m (vs $24.4m previously). After including Q318 net cash of $13.0m, we obtain an equity valuation of $23.9m, or $3.66 per FD share.

Financials: Funded to early 2020

Atossa had $13.0m net cash at 30 September 2018 and we continue to expect its total current funds on hand to last into early 2020. We continue to assume that Atossa will raise $10m in 2019 to fund its operations, and as per our usual policy, for modelling purposes, we assign these financings to long-term debt.

Sensitivities: Development risks, partnerships

For both the endoxifen and the IDMC-fulvestrant programs, development may hinge on future FDA guidance on whether the projects can fall under the 505(b)2 development pathway. This would reduce the breadth of required clinical data needed to support a marketing application and we assume the projects are under this pathway in our model. For MBD and gynecomastia, commercialization success may depend on the educational and marketing efforts needed to convince at-risk patients of the benefits of local therapy. For oral endoxifen, stakeholders must be persuaded of benefits of the product versus oral tamoxifen in patients refractory to oral tamoxifen.

Multiple approaches aimed at improving breast health

Atossa's strategy is to develop therapies for the prevention or treatment of breast cancer in women, and to treat gynecomastia (male breast enlargement) in men. The lead candidate is endoxifen, which is being developed in both oral and topical formulations. The firm has positioned topical endoxifen as a potential treatment for both MBD, a condition associated with increased risk for the development of breast cancer, as well as for gynecomastia. Oral endoxifen is being developed to prevent cancer recurrence in patients refractory to tamoxifen. A Phase II MBD study is already underway, with results expected in Q219, and the firm plans to start Phase II studies in H119 in the two other indications (oral for preventing recurrence tamoxifen-refractory patients, and topical for gynecomastia). Atossa is also involved with a Phase II trial using its proprietary IDMC to deliver fulvestrant, an approved metastatic breast cancer drug marketed by AstraZeneca, to treat ductal carcinoma in-situ (DCIS) and potentially other breast cancers.

Endoxifen may provide advantages to tamoxifen

Tamoxifen is well established for the treatment and prevention of breast cancer, given its association with ER antagonistic effects, but such effects are only realized by a few of tamoxifen's active metabolites, and not by the parent molecule itself. When dosed orally, tamoxifen is metabolized in the liver into multiple metabolites, the most significant of which (in terms of ER antagonism contribution and plasma concentration in patients with normal tamoxifen metabolism) are endoxifen (4-hydroxy-N-desmethyltamoxifen) and, to a lesser extent, afimoxifene (4-hydroxytamoxifen). Atossa has since secured drug manufacturing supply, developed topical and oral endoxifen formulations and filed composition of matter and methods of treatment patent applications (with patent lives potentially into 2036)

Atossa believes that administering endoxifen can provide several advantages compared to tamoxifen. If a topical formulation of endoxifen can deliver significant targeted amounts of drug to breast tissue with minimal systemic absorption, it could potentially play a meaningful therapeutic role by providing the local ER antagonistic therapeutic activity associated with tamoxifen, while reducing the risks of systemic adverse events (AE) associated with the oral drug, such as thromboembolic events. This could make the topical form more amenable for chronic use indications in the absence of a prior breast cancer diagnosis, such as MBD or gynecomastia.

Oral endoxifen is being primarily developed to prevent cancer recurrence in women who do not benefit from taking (or who are refractory to) oral tamoxifen, often due to a genetic predisposition that impairs their tamoxifen metabolism.

MBD presents potentially untapped prevention market

Breast tissue consists of lobules (glands), ducts, and fatty and fibrous connective tissue; generally, dense breast tissue has higher quantities of fibrous or glandular tissue and less fat content. For most women, breasts become less dense with age. According to the Breast Imaging Reporting and Data System (BI-RADS) defined by the American College of Radiology (ACR), there are four degrees of breast density composition (see Exhibit 2 below)

Exhibit 2: Breast density categories

Type	Description
A	The breasts are almost entirely fatty
B	There are scattered areas of fibroglaundular density
C	The breasts are heterogeneously dense, which may obscure small masses
D	The breasts are extremely dense, which lowers the sensitivity of mammography

Source: American College of Radiology

Tamoxifen is the only known approved prescription product that has been unequivocally shown to reduce breast density[1] although it has not been approved by FDA for this purpose. Due in part to the risks for AE, tamoxifen has not generally been employed for MBD reduction (in women who have not had breast cancer). Some studies suggest that oral acetylsalicylic acid or other anti-inflammatories may reduce MBD too, but other studies have not found such an association.[2]

High breast density linked to increased cancer risk

A topical treatment with tamoxifen-like effects for reducing MBD and possibly few side effects could have a meaningful chemo-preventative market, as a recent US study following over 202,000 women found that MBD is a significant independent predictor for increased breast cancer risk.[3] The study examined multiple criteria in addition to MBD, including first-degree family history of breast cancer, body mass index, history of benign breast biopsy, and age at first childbirth. Among these, the study found MBD was the most prevalent risk factor for both premenopausal and postmenopausal women. It found that 39.3% of premenopausal and 26.2% of postmenopausal breast cancers could potentially be averted if all women with heterogeneously or extremely dense breasts (BI-RADS C or D) shifted to scattered fibroglandular breast density (BI-RADS B).

Topical endoxifen Phase II MBD study reaches full enrolment

Atossa is conducting a double-blinded, placebo-controlled Phase II study of its topical endoxifen formulation in women with elevated MBD at Stockholm South General Hospital in Sweden (affiliated with Karolinska Institute). The study follows a Phase I trial completed in Q317 showing that topical endoxifen was safe and well tolerated in women and that it can generate increase is blood endoxifen in a dose-dependent manner.

The current trial is being led by principal investigator Dr Peter Hall, and the primary endpoint is to determine if daily topical endoxifen administration results in changes in MBD, which will be measured after three and six months of study commencement. The secondary endpoints are safety and tolerability. Enrollment was completed in October 2018, and 90 participants were randomized to one of three 30-participant groups (one placebo arm and two endoxifen dosage arms). If the study shows a reduction in MBD, data will be used to drive sample size calculations for a future pivotal Phase III study. We anticipate that study results should be available in Q219.

Skin irritations with topical formulation adds uncertainty

Atossa disclosed in November 2018 that some participants in the current MBD Phase II study have reported skin rashes and irritation and have withdrawn from the trial. Skin reactions were also observed in the Phase I study, but were not reported as a significant safety or tolerability concern. The study investigators are continuing to evaluate the scope, extent and nature of the skin reactions, as well as evaluating approaches to reduce skin reactions and maximize participation in the trial. Atossa cautions that additional study participants could experience these and/or other

[1] Cuzick J, Warwick J, Pinney E et al. J Natl Cancer Inst. 2004 Apr 21;96(8):621-8

[2] McTiernan A, Wang CY, Sorensen B, et al. Cancer Epidemiol Biomarkers Prev. 2009 May;18(5):1524-30.

[3] Engmann NJ, Golmakani MK, Miglioretti DL et al. JAMA Oncol. 2017 Sep 1;3(9):1228-1236

more serious side effects during the trial, which could potentially impede its successful completion. Altogether, it is premature to speculate on whether or not the skin reactions observed to date will require a formulation change for future clinical development (leading to product development delays), or whether the same reaction would occur in men with the existing formulation.

Male topical endoxifen program to advance to Phase II

In September 2018, Atossa reported positive safety results from its Phase I dose escalation study on topical endoxifen in men. The study was a 24-patient trial where healthy male volunteers were provided repeat doses of topical endoxifen for 28 days. There were three cohorts (dosed at 1mg/breast, 3mg/breast, and 5mg/breast), and with each cohort comprised of six individuals receiving treatment and two obtaining placebo. Atossa reported that topical endoxifen was well tolerated at all tested dose levels, there were no clinically significant safety signals and no clinically significant AEs among the treated study participants. Atossa plans to retain a contract research organization (CRO) in Q418 for an upcoming Phase II study using topical endoxifen in men starting prostate cancer therapy to prevent or reduce gynecomastia and/or improve quality of life. We expect the Phase II study will begin in H119.

No systemic absorption versus results from prior female topical Phase I

A notable finding in the male study is that that patient blood samples showed there was no measurable plasma endoxifen in any of the dose ranges. This suggests a topical mode of administration may not necessarily raise blood endoxifen, thus suggestive of safety, but also may raise a question as to whether the topical administration delivers a sufficient amount of drug to the breast tissue in men. In contrast, as stated earlier, the firm's Phase I topical endoxifen trial in women (reported Q317) showed measurable blood endoxifen levels increases in a dose-dependent manner (and the same dosage ranges were used as in the male study).

Thus, the female Phase I study may have provided a stronger suggestion that endoxifen may cross the skin barrier when applied daily to the breast; the premise being that following skin contact, endoxifen would reach breast tissue and exert a therapeutic effect by binding ER in the region, with some proportion of the endoxifen absorbed by the vascular structure and reaching systemic circulation. In the male topical study, because plasma endoxifen did not rise, there is less evidence thus far of local drug absorption.

One possible explanation for the differences between plasma endoxifen measures between the male and female topical studies is that tamoxifen (of which endoxifen is a metabolite) may be metabolized significantly faster in men; Dickschen et al. found that tamoxifen is metabolized significantly faster in male rats compared to female rates (by a factor of two to threefold after 24 hours).[4]

Review of gynecomastia opportunity

Gynecomastia is male breast enlargement and is fairly common, occurring in 50–60% of adolescents (it is often transitory in this age group), and up to 70% of men aged between 50 and 69 years.[5] Symptomatic gynecomastia, with accompanying pain, occurs much less frequently and hence, relatively few gynecomastia patients, as a percentage, seek treatment. Gynecomastia is often caused by a hormone imbalance where testosterone is low compared to estrogen, and can be precipitated by certain prescribed medications, including androgen deprivation therapy (to treat prostate enlargement and prostate cancer), anti-anxiety medication and certain cancer treatments and heart medications. One of the most significant symptomatic populations are men experiencing

[4] Dickschen K, Willmann S, Thelen K, et al. Front Pharmacol. 2012 May 21;3:92.

[5] Johnson RE, Kermott CA, Murad MH. Ther Clin Risk Manag. 2011;7:145-8.

anti-androgen treatment (such as bicalutamide or flutamide) for prostate cancer, as up to 70% of these patients experience gynecomastia.[6] About 16% of prostate cancer patients taking anti-androgen therapy discontinue their treatment primarily due to the gynecomastia.[7]

There are no FDA-approved therapeutics for gynecomastia, although SERM drugs such as tamoxifen and raloxifene, and aromatase inhibitors (such as testolactone) have been used off-label. Topical endoxifen can potentially provide tolerability and safety advantages compared to oral tamoxifen, given the expectation of lower systemic drug exposure, as prolonged systemic tamoxifen usage has been associated with the development of fatty liver disease in up to one-third of patients.[8] Topical endoxifen may also have specific advantages for patients experiencing gynecomastia from prostate cancer therapy, as oral tamoxifen has been shown to raise serum testosterone,[9] which is counterproductive and undesired in most cases of prostate cancer.

Although topical endoxifen therapy may potentially provide several benefits over current oral off-label SERM drugs such a tamoxifen, a recent review study[10] reported that less than 4% of men taking oral tamoxifen for gynecomastia stopped taking the drug for toxicity reasons. The review study assessed tamoxifen use in men across 14 randomized clinical trials and 39 non-randomized studies found that the most common AEs in men from tamoxifen therapy were gastrointestinal, cardiovascular issues and psychiatric disorders.

Oral endoxifen for reducing cancer recurrence risk

Following surgical treatment for atypical hyperplasia (AH) or non-invasive ER+ breast cancers, additional oral treatment with a SERM drug such as tamoxifen or raloxifene (Evista) is often recommended. Approximately 75–80% of breast cancers are ER+[11] (ie they grow in response to estrogen). A large-scale randomized study (IBIS-I), where over 7,000 women (aged 35–70 with elevated breast cancer risk) were randomized to five years of tamoxifen vs placebo, found that tamoxifen reduced ER+ breast cancer incidence in high-risk women by 30–50% over five years of treatment. IBIS-I found that after a median follow up of 16 years, tamoxifen-treated patients had a 7.0% risk of developing breast cancer, versus 9.8% in the placebo group. The reduction in ER+ invasive breast cancer was maintained for at least 11 years after cessation of tamoxifen.[12] The American Society of Clinical Oncology now recommends consideration of adjuvant tamoxifen therapy for 10 years.[13] Despite evidence of reduced ER+ breast cancer risk, SERM use has been limited to less than 1% of AH patients,[14] with the low uptake attributed to patient's fears of AE of SERM drugs.

Up to 20% of patients taking tamoxifen may not benefit from drug

The case for using oral endoxifen to reduce risk of recurrence (instead of tamoxifen) results from several research groups having found that patients with deficiencies in certain liver cytochrome

[6] Fagerlund A, Cormio L, Palangi L et al. PLoS One. 2015 Aug 26;10(8):e0136094

[7] Heidenreich A, Bastian PJ, Bellmunt J, et al. European urology 2014;65(2):467–479

[8] US National Institutes of Health. https://livertox.nih.gov/Tamoxifen.htm

[9] Birzniece V, Sata A, Sutanto S, et al. J Clin Endocrinol Metab. 2010 Dec;95(12):5443–8.

[10] Wibowo E, Pollock PA, Hollis N, et al. Andrology. 2016 Sep;4(5):776–88.

[11] Onitilo AA, Engel JM, Greenlee RT, et al. Clin Med Res. 2009 Jun; 7(1-2): 4–13.

[12] Cuzick J, Sestak I, Cawthorn S, et al. LancetOncol 16 (1): 67–75, 2015.

[13] https://www.asco.org/about-asco/press-center/news-releases/asco-guideline-update-recommends-tamoxifen-10-years-women-non

[14] Waters EA, McNeel TS, Stevens WM, et al. Breast Cancer Res Treat. 2012 Jul;134(2):875–80

P450 enzymes (due to genetic factors, medication interactions or other factors) have an impaired ability to metabolize tamoxifen into endoxifen. Up to 15–20% of Europeans carry genetic P450 CYP2D6 variants associated with an impairment in forming anti-estrogenic tamoxifen metabolites.[15] Multiple study groups (Fox, Madlensky, Saladores) have found that in patients taking tamoxifen, those with the lowest amounts of systemic endoxifen (resulting presumably from impaired tamoxifen metabolism) have a higher risk of cancer recurrence (between 35% and 60% higher risk, depending on the study) than the remaining tamoxifen-treated patients.[16,17] From this it is hypothesized that dosing oral endoxifen (instead of tamoxifen) could provide benefits in such patients.

Atossa conducted an oral endoxifen Phase I study in 2017 and results showed, after 21 days of daily dosing, each of the three tested oral arms (1mg/day, 2mg/day, 4mg/day) led to plasma endoxifen levels well in excess of 30nmol/L, and the plasma concentration was dose-dependent (39.8nmol/L for the 1mg/day arm, rising to 187.8nmol/L for the 4mg/day arm). Fox et al. suggest that 15nmol/L of endoxifen may be the critical level needed for anticancer effect.[18] Atossa is advancing the oral formulation to Phase II for preventing cancer recurrence in patients refractory to tamoxifen, and it expects to finalize the study design and select the CRO in Q418. We expect the Phase II study will commence in H119.

Earlier attainment of steady state levels vs oral tamoxifen

Atossa also examined the steady state levels of plasma endoxifen concentration after multiple doses. In February 2018, it reported additional data from its Phase I study, suggesting the median time for patients in the study to reach the steady-state serum endoxifen levels while taking daily oral doses was seven days. Atossa reports that published literature[19] indicates that it takes 50–200 days for patients to reach steady-state blood endoxifen levels when taking daily doses of oral tamoxifen.

Based on this, Atossa believes that oral endoxifen may provide steady-state plasma therapeutic endoxifen levels weeks or even months earlier than oral tamoxifen, which may potentially provide a more rapid onset of therapeutic effect (in terms of retarding ER+ breast cancer) than oral tamoxifen for recurrence prevention. While we believe it could be challenging to prove that the more rapid onset of steady-state blood levels can lead to a statistically significant improvement in outcomes, Atossa started a pilot Australia-based study in July 2018 to assess using oral endoxifen (for at least 21 days) in the 'window of opportunity' between ER+ breast cancer diagnosis and surgery (in patients requiring mastectomy or lumpectomy). The primary endpoint is to determine if the administration of oral endoxifen reduces the tumor activity as measured by Ki-67, which is a marker of cellular proliferation. The study plans to recruit eight patients and if at least two of these show a Ki-67 response (suggestive of tumor activity reduction), it will be increased to 25 subjects. The secondary endpoints are safety and tolerability and assessment of the study drug on expression levels of both estrogen and progesterone receptors. As the effectiveness of such a treatment (endoxifen in the 'window of opportunity' between diagnosis and surgery) is largely hypothetical at this stage, in our view, we have not explicitly included this treatment approach in our oral endoxifen forecasts.

[15] Engmann NJ, Golmakani MK, Miglioretti DL, et al. JAMA Oncol. 2017 Sep 1;3(9):1228–1236

[16] Madlensky L, Natarajan L, Tchu S, et al. ClinPharmacolTher. 2011 May; 89(5):718–25.

[17] Saladores P, Mürdter T, Eccles D, et al. The Pharmacogenomics Journal (2015) 15, 84–94

[18] Fox P, Balleine RL, Lee C, et al. Clin Cancer Res. 2016 Jul 1; 22(13):3164-71.

[19] Atossa Genetics press release dated 1 February 2018.

NCI/Mayo Clinic group activity on endoxifen could provide competition

A team of investigators at Mayo Clinic (Matthew Goetz, Matthew Ames and collaborators) and the National Cancer Institute (NCI) is studying its own formulation of endoxifen hydrochloride in treating patients with ER+ breast cancer (but negative for HER receptors). While Atossa is filing patents for its own endoxifen formulations and methods of treatment, there is a risk that competing studies from the Mayo/NCI investigators, should they lead to registration or commercialization-stage end-products, could lead to intellectual property (IP)-related competition challenges to Atossa's eventual oral endoxifen product.

IDMC-fulvestrant and CAR-T program opportunities

Atossa continues its Phase II trial using its proprietary IDMC to deliver fulvestrant, an approved metastatic breast cancer drug marketed by AstraZeneca, to treat DCIS, and potentially other breast cancers. Fulvestrant (marketed as Faslodex by AstraZeneca) is FDA-approved for ER+ metastatic breast cancer (with $941m in global 2017 sales, up 14% y-o-y) and is normally administered by intramuscular (IM) injection usually consisting of a monthly dose of two injections (costing $10,000–14,000 a month in the US).

In March 2016, Atossa initiated a 30-patient, open-label Phase II study on IDMC-administered fulvestrant and transferred the study site from Columbia University Medical Center to the Montefiore Medical Center in New York City in early 2017. The company has not provided guidance as to when it expects to complete recruitment.

The firm is also investigating the use of its IDMC to deliver potential CAR T-cell therapies (CAR-T therapies) directly to the site of breast cancer, through a process it refers to as Transpapillary CAR-T Delivery (TRAP CAR-T). Atossa believes its IDMC could potentially provide preferential and more targeted delivery of CAR-T therapies to the breast ducts, the site of the majority of early-stage breast cancers, and thereby potentially improve efficacy while reducing off-site and systemic toxicity (such as 'cytokine storms' associated with therapy). Atossa is still in the research/preclinical stage of the TRAP CAR-T platform and will need to partner with a developer of CAR-T immunotherapy, as its involvement will be primarily at the drug-delivery level, while relying on the pharmacological and immunology expertise of a would-be partner for the 'active treatment' component of the planned TRAP CAR-T therapies.

Financial forecasts

Atossa is developing endoxifen across several areas. Our model previously included topical endoxifen treatment of MBD (topical for women) and oral endoxifen for the prevention of breast cancer recurrence in tamoxifen-refractory patients, as the largest potential value-generating opportunities for Atossa. We now also include consideration in our model for the topical formulation's opportunity in gynecomastia, as this program is now advancing to Phase II.

We assume that Atossa will out-license the oral and topical endoxifen programs in all indications in H219, on the conclusion of the planned Phase II studies for the three indications above, and it will be entitled to 20% royalties on net sales. Of course, if the skin irritation issues raised in the current ongoing Phase II MBD study require a change in the product candidate's formulation, this could impede partnership discussions and/or add delays such as the need for new clinical studies.

At this point, we have not changed our revenue or timing forecasts for topical endoxifen for the treatment of MBD and they are reiterated below. Following a subsequent pivotal study (to be funded by the partner), topical endoxifen in MBD could be launched in 2021. We continue to estimate the

potential target market for topical endoxifen for MBD prevention is 10% of women above age 40[20] (this collective group will fall in the highest category of MBD, BI-RADS grade D) and that peak market share would be 15% of the target market, such that in the year of peak sales (2026) about 195,000 US women would be obtaining therapy, leading to US sales of $523m (worldwide sales of $922m), and worldwide net royalties of $184m (in 2026).

Exhibit 3: Topical endoxifen revenue forecasts in MBD

Year-end 31 December	2021	2022	2023	2024	2025	2026
US market						
Estimated population of women above age 40 (000)*	92,742	94,141	95,561	97,003	98,466	99,952
High breast density proportion (%)**	10	10	10	10	10	10
Proportion with mammography test in past two years (%)	65	65	65	65	65	65
Estimated number of years between treatment cycle	5	5	5	5	5	5
Market share (%)	0.9	2.5	4.9	8.3	12.6	15.0
Number of patients undergoing treatment at year-end	10,868	30,777	61,069	104,094	160,871	194,906
Net price per treatment cycle ($)	2,430	2,479	2,528	2,579	2,630	2,683
Total topical endoxifen revenue ($000)	26,463	76,377	154,529	268,628	423,360	522,911
Royalty rate (%)	20	20	20	20	20	20
Net revenue to Atossa ($00)	5,293	15,275	30,906	53,726	84,672	104,582
Europe and ex-US markets						
Total topical endoxifen revenue ($000)	20,220	58,360	118,076	205,261	323,493	399,560
Royalty rate (%)	20	20	20	20	20	20
Net revenue to Atossa ($00)	4,044	11,672	23,615	41,052	64,699	79,912
Worldwide topical endoxifen sales ($000)	46,683	134,737	272,605	473,889	746,853	922,471
Worldwide topical endoxifen royalties to Atossa ($000)	9,337	26,947	54,521	94,778	149,371	184,494

Source: Edison Investment Research. Note: *Based on US Census data.**Estimated prevalence of BI-RADS Class D is over 7% in patients above age 40 according to Sprague BL, Gangnon RE, Burt V, et al. J Natl Cancer Inst. 2014 Oct; 106(10). We assume a proportion of patients within BI-RADS Class C may also be considered as having high MBD. This explains our assumption that 10% of women above age 40 (who undergo periodic mammography testing) could be potential MBD treatment candidates.

We have pushed back our commercialization timelines for the company's oral endoxifen formulation in tamoxifen-refractory patients, given that the Phase II study in this indication had not yet begun and we previously anticipated commencement in or around mid-2018. Beyond the planned Phase II study, we assume that an additional (pivotal) study would be required for approval of the oral drug, and we believe it would start in late 2019 (vs Q418 or H119, in our prior estimates), and hence we now expect that the earliest time oral endoxifen can reach the market would be in H221 (2020 previously).

Based on findings from Madlensky and Fox, we continue assume that 20% of the 300,000 US women (and approximately one million women worldwide) currently taking tamoxifen[21] do not achieve sufficient plasma endoxifen concentrations, and thus reflect the potential target market for Atossa's oral endoxifen (thus 60,000 persons in the US). Of these, we assume a peak market share of 50% of this group, which would be attained by 2026 (vs 2025 previously), with peak net sales of $94m in the US ($166m worldwide), which leads to global net royalties to Atossa of $33m in 2026.

We have not modified our forecast for the IDMC-fulvestrant program, which has been in a Phase II study since 2016. For IDMC-fulvestrant we continue to assume a potential launch in 2023, with worldwide peak sales (consisting of the IDMC device and separate from the cost of fulvestrant) of $182m in 2026, with royalties to Atossa of $36.5m (20% assumed royalty rate).

We are now introducing revenue forecasts for the gynecomastia (topical endoxifen) indication, given that this program is advancing to Phase II studies. We assume this program will be partnered (as with the MBD indication) and that following the planned Phase II study, a partner will commence

[20] Over 95% of breast cancers occur in women above age 40 and hence we assume that younger women will not be part of the MBD treatment populations

[21] Waters EA, McNeel TS, Stevens WM et al. Use of tamoxifen and raloxifene for breast cancer chemoprevention in 2010 (2012). Cancer Prevention Faculty Publications. Paper 6. http://digitalcommons.wustl.edu/canpre_pubs/6.

a registration-enabling study, which can lead to market launch in 2022. We assume that about 12.5 million men in the US have gynecomastia, but only 7.5% of these have clinically symptomatic levels (causing pain and/or discomfort or unease) that prompt the patients to seek treatment, and that topical endoxifen will have a peak market share of about 15% among such patients (given that tamoxifen is already being used off-label in such patients, with relatively few patients discontinuing treatment due to AE). Peak global sales (2027) for topical endoxifen in gynecomastia are estimated at $691m, leading to $138m in royalties to Atossa that year.

Exhibit 4: Topical endoxifen revenue forecasts in male gynecomastia

Year-end 31 December	2022	2023	2024	2025	2026	2027
US market						
Estimated population men aged 50–70 (000)	40,178	40,328	40,478	40,629	40,781	40,933
Percentage of such men with gynecomastia (%)	25	25	25	25	25	25
Men aged 50–70 with gynecomastia (000)	10,044	10,082	10,120	10,157	10,195	10,233
Other males with gynecomastia (000)	2,511	2,520	2,530	2,539	2,549	2,558
Total US males with gynecomastia (000)	12,556	12,602	12,649	12,697	12,744	12,791
Percentage who are symptomatic and seek treatment (%)	7.5	7.5	7.5	7.5	7.5	7.5
Total potential US treatment population (000)	942	945	949	952	956	959
Average yearly market share of topical endoxifen (%)	1.1	3.3	6.3	9.3	12.6	14.9
Net yearly treatment price ($) per patient	2,485	2,532	2,581	2,632	2,684	2,737
Total topical endoxifen revenue ($000)	26,225	78,611	155,292	233,711	322,540	391,612
Royalty rate (%)	20	20	20	20	20	20
Net revenue to Atossa ($000)	5,245	15,722	31,058	46,742	64,508	78,322
Europe and ex-US markets						
Total topical endoxifen revenue ($000)	20,039	60,067	118,660	178,580	246,455	299,234
Royalty rate (%)	20	20	20	20	20	20
Net revenue to Atossa ($00)	4,008	12,013	23,732	35,716	49,291	59,847
Worldwide topical endoxifen sales ($000)	46,263	138,678	273,951	412,291	568,996	690,846
Worldwide topical endoxifen royalties to Atossa ($000)	9,253	27,736	54,790	82,458	113,799	138,169

Source: Edison Investment Research

For all endoxifen indications, we assume the company will partner the product (in H219) and afterwards, the partner will be responsible for registration-enabling clinical studies (which we continue to assume will fall under the 505(b)2 registration pathway).[22]

Financials

Atossa reported Q318 results on 14 November 2018, with a net loss of $3.3m (the net loss for the first three quarters of 2018 was $9.3m excluding a $11.5m dividend attributable to preferred stock holders)[23] and an operating cash burn rate of $2.3m for the quarter ($6.5m for the first nine months of 2018). Q318 R&D costs were $1.42m, down slightly from $1.47m in Q218. The majority of R&D costs were due to the clinical endoxifen programs underway and under planning. We expect the current R&D cost rate to be maintained or potentially increase through at least Q219, given the increased size and scope of current and planned Phase II endoxifen studies. Q318 G&A costs were $1.9m, up 46% year-on-year (excluding depreciation expense), with the increases due primarily to higher payroll costs, stock-based compensation expense and staff bonus payments.

Following Q318 results and given the delay in the commencement of the tamoxifen-refractory oral endoxifen Phase II study (vs our prior estimate), we have lowered our 2018 R&D expenses but

[22] As tamoxifen has a long-established history of systemic use, and as endoxifen is a metabolite of this drug, we expect that Atossa (or the eventual endoxifen sub-licensee) would be able to pursue FDA approval through the 505(b)2 registration pathway, whereby the extent of efficacy data needed for registration is less substantive or onerous than through a traditional New Drug Application, or 505(b)1, pathway. This should shorten the amount of time needed for a registration study.

[23] Atossa Genetics had issued convertible preferred shares and warrants as part of a Q218 equity financing initiative, and the accounting treatment of the convertible preferred shares prompted the issuance of an $11.5m deemed dividend to the preferred shareholders in the first nine months of 2018.

increased our 2019 assumptions. We model that all endoxifen clinical study costs after 2019 will be paid by the future licensee partner. We now expect FY18 and FY19 R&D expenses of $5.5m and $6.6m, vs our prior forecasts of $7.0m and $4.0m, respectively. We have increased 2018 and 2019 G&A expense forecasts to $7.4m and $5.1m, respectively, versus our prior estimates of $4.4m and $3.0m, respectively. We have also raised our G&A cost estimates for future years.

Given the above, we now assume an operating cash burn rate (excluding net interest income) of $10.7m in 2018 and $8.7m in 2019, versus our prior estimates of $12.1m and $6.8m respectively. We believe the burn rate will decrease after 2019, as we model the company to have partnered the endoxifen programs (oral and topical) in H219, which would reduce its R&D expense needs. Of course, if the skin irritation/rash issues suggested in the preliminary endoxifen responses in the Phase II MBD study persist and a formulation revision becomes desirable or required, this could impede or delay the realization of a partnership agreement, and may result in the need to raise more funds to internally develop the endoxifen program further prior to a partnership transaction.

Atossa had $13.0m net cash at 30 September 2018 and we expect its total current funds on hand to last into early 2020. We continue to assume that Atossa will raise $10m in 2019 to fund its operations, and as per our usual policy, for modeling purposes, we assign these financings to long-term debt.

Valuation: Equity valuation of $23.9m

Our rNPV valuation continues to include the prospects of the company's topical and oral endoxifen programs for women, and its IDMC-delivered fulvestrant program. Given that the gynecomastia endoxifen program is advancing to Phase II studies, we are now also including its revenue potential in our valuation forecasts, although we only apply a 4% probability of success given that the candidate has not yet demonstrated proof-of-concept for reducing gynecomastia in men, and given the potential skin irritation issues suggested in the ongoing MBD study with the current topical formulation. We continue to apply a 20% probability of success estimate for the oral endoxifen program.

We have lowered our probability of success for the topical MBD endoxifen program to 4% (from 5% previously) given the skin irritation issue that has been raised and that this may provoke development delays beyond our current assumptions. We also reiterate proof-of-concept in terms of MBD reduction has not been shown and our forecasts depend on building significant support and recognition among patients, physicians and stakeholders of the benefits of treating MBD as a preventative approach to lowering cancer risk. Our 10% success probability estimate for the IDMC-fulvestrant program is unchanged.

Exhibit 5: Atossa Genetics rNPV assumptions

Product contributions (net of R&D costs)	Indication	rNPV ($m)	rNPV/ share ($)	Probability of success	Launch year	Peak US market share	Peak WW sales (US$m)
Topical endoxifen	High breast density	17.7	2.71	4.0%	2021	15%	922 in 2026
Topical endoxifen	Gynecomastia	10.9	1.67	4.0%	2022	15%	691 in 2027
Oral endoxifen	Breast cancer	16.9	2.58	20.0%	H221	12.5% of patients taking tamoxifen	166 in 2026
Intraductal Microcatheter (for Fulvestrant)	Breast cancer	8.0	1.23	10.0%	H222	25%	182 in 2026
Corporate costs & expenses							
SG&A expenses		(37.2)	(5.70)				
Net capex, NWC & taxes		(5.3)	(0.82)				
Total rNPV		10.9	1.67				
Net cash/(debt) (Q318e)		13.0	1.99				
Total equity value		23.9	3.66				
FD shares outstanding (000)*		6,522					

Source: Edison Investment Research. Note: *Includes adjustment for dilutive effect of 3,517 Series B convertible preferred shares by assuming their full conversion into 1.0m common shares.

We continue to apply a 12.5% discount rate in our rNPV approach. After increasing our G&A cost estimates and introducing gynecomastia forecasts, we now obtain an rNPV valuation of $10.9m, below our prior valuation of $24.4m. After including Q318 net cash of $13.0m, we obtain an equity valuation of $23.9m, or $3.66 per FD share (which assumes full conversion of 3,517 currently outstanding Series B convertible preferred shares into 1.0m common shares).[24]

Sensitivities

Development and regulatory risk: to gain approval, endoxifen and IDMC-fulvestrant must be shown to be safe without any notable safety concerns. There are preliminary concerns in the current Phase II MBD study that the current topical endoxifen formulation may cause skin irritation or rashes which, if confirmed, may require formulation revisions that could add developmental delays and/or may reduce product effectiveness. To be commercially successful, Atossa's products must also show signals of therapeutic efficacy. The development strategies for both programs also depend on whether the FDA agrees to the firm's proposed regulatory pathway (505(b)2), rather than the standard (505(b)1) NDA application process, or PMA for IDMC-fulvestrant. Should the FDA require the standard application processes (needing more exhaustive clinical data), the additional resource and time requirements could have an impact on the firm's ability to continue such programs and/or weigh on our valuation. The potential for drug transference risk (gel rubbing off on clothing and the possible risk of topical endoxifen exposure to family members) may also be considered by the regulators.

Commercial and competition risk: even if endoxifen obtains regulatory approval, much of its success will hinge on the marketing capabilities of a would-be partner. Currently, tamoxifen's share for breast cancer prevention in at-risk patients remains very low, due to concerns of systemic side effects. Endoxifen's success will depend largely on the marketing and educational efforts of the partner to persuade healthcare providers and patients of the drug's potential uses and benefits (and in the case of topical endoxifen, of the benefit of reducing MBD). Further, the product will need to compete with other preventative cancer products, most notably aromatase inhibitors in post-menopausal women, as well as other potential emerging products. Commercial success will depend on relative performance (in reduction of recurrence rates, safety, etc).

Partnership risk: we believe Atossa will require development partners to advance endoxifen or IDMC-fulvestrant through pivotal studies and to support the marketing activities required to raise a

[24] Each Series B Convertible preferred share is convertible to 284 common shares

sufficient profile for these products. Challenges to securing viable partnerships could lead to unnecessary development delays and/or unfavorable terms.

Financing risk: Atossa's current funds on hand are expected to only be sufficient into early 2020. We are modelling that the company will raise $10m in 2019 to strengthen its balance sheet and build a financial buffer. After this point, we expect partners to fund the therapeutic programs in endoxifen and fulvestrant. While our model accounts for the anticipated 2019 financing as long-term debt, the firm most likely will need to issue equity instead. If this is the case, there is the risk of significant dilution to shareholders if pricing terms are not favorable.

Intellectual property and litigation risk: the success of Atossa's programs will depend on its ability to defend the intellectual property (IP) assets surrounding its technologies. For oral endoxifen, different research groups are developing oral formulations and there may be IP challenges if these groups' advancements lead to approved commercial products. The IDMC-fulvestrant program may also need to contend with legal challenges from AstraZeneca, if it does not support or enter a partnership with Atossa on IDMC-fulvestrant. AstraZeneca could perceive the IDMC-fulvestrant program as a competitive threat and could seek legal action to impede its development.

Exhibit 6: Financial summary

US$000s	2015	2016	2017	2018e	2019e	2020e
31-December	IFRS	IFRS	IFRS	IFRS	IFRS	IFRS
PROFIT & LOSS						
Revenue	2	0	0	0	0	0
Cost of Sales	(132)	0	0	0	0	0
General & Administrative	(9,996)	(6,176)	(4,730)	(7,438)	(5,100)	(5,202)
Research & Development	(2,360)	(770)	(2,328)	(5,490)	(6,600)	(1,750)
EBITDA	(9,484)	(6,946)	(7,058)	(12,927)	(11,700)	(6,952)
Depreciation	(273)	(303)	(129)	(39)	(44)	(48)
Amortization	0	0	0	0	0	0
Operating Profit (before exceptionals)	(9,756)	(7,250)	(7,187)	(12,966)	(11,744)	(7,000)
Exceptionals	0	881	(935)	0	0	0
Other	(3,002)	0	0	0	0	0
Operating Profit	(12,758)	(6,369)	(8,123)	(12,966)	(11,744)	(7,000)
Net Interest	0	0	0	49	71	(22)
Profit Before Tax (norm)	(9,756)	(7,250)	(7,187)	(12,917)	(11,673)	(7,022)
Profit Before Tax (FRS 3)	(12,758)	(6,369)	(8,123)	(12,917)	(11,673)	(7,022)
Tax	0	0	0	0	0	0
Profit After Tax and minority interests (norm)	(9,756)	(7,250)	(9,756)	(17,698)	(11,673)	(7,022)
Profit After Tax and minority interests (FRS 3)	(12,758)	(6,369)	(10,691)	(17,698)	(11,673)	(7,022)
Average Number of Shares Outstanding (m)	0.2	0.2	1.0	4.1	6.2	7.2
Share options and other dilutive equity outstanding (m)	0.0	0.0	0.0	1.0	1.0	1.0
EPS - normalised ($)	(61.78)	(29.52)	(10.01)	(4.31)	(1.88)	(0.97)
EPS - normalised and fully diluted ($)	(61.78)	(29.52)	(10.01)	(4.31)	(1.88)	(0.97)
EPS - (IFRS) ($)	(80.78)	(25.93)	(10.97)	(4.31)	(1.88)	(0.97)
Dividend per share ($)	0.0	0.0	0.0	0.0	0.0	0.0
BALANCE SHEET						
Fixed Assets	1,948	890	266	191	208	226
Intangible Assets	1,701	640	76	55	55	55
Tangible Assets	248	249	190	136	152	171
Current Assets	4,295	3,255	7,898	9,792	11,068	7,053
Short-term investments	275	55	55	55	55	55
Cash	3,716	3,028	7,217	8,805	10,081	6,065
Other	304	172	626	932	932	932
Current Liabilities	(2,502)	(1,047)	(1,225)	(3,005)	(3,005)	(3,005)
Creditors	(2,502)	(1,047)	(1,225)	(3,005)	(3,005)	(3,005)
Short term borrowings	0	0	0	0	0	0
Long Term Liabilities	0	0	0	0	(10,000)	(10,000)
Long term borrowings	0	0	0	0	(10,000)	(10,000)
Other long term liabilities	0	0	0	0	0	0
Net Assets	3,742	3,097	6,939	6,979	(1,729)	(5,726)
CASH FLOW						
Operating Cash Flow	(13,953)	(5,375)	(6,594)	(10,698)	(8,735)	(3,928)
Net Interest	0	0	0	49	71	(22)
Tax	0	0	0	0	0	0
Capex	(131)	(9)	0	(54)	(60)	(66)
Acquisitions/disposals	(158)	0	0	0	0	0
Financing	9,457	4,696	10,783	12,291	0	0
Net Cash Flow	(4,785)	(688)	4,190	1,587	(8,724)	(4,016)
Opening net debt/(cash)	(8,501)	(3,991)	(3,083)	(7,272)	(8,860)	(136)
HP finance leases initiated	0	0	0	0	0	0
Other	275	(220)	0	0	0	0
Closing net debt/(cash)	(3,991)	(3,083)	(7,272)	(8,860)	(136)	3,880

Source: Edison Investment Research, company reports

Contact details	Revenue by geography
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Management team

Chairman and CEO: Steven C Quay, MD, PhD	Chief financial officer and counsel/secretary: Kyle Guse, CPA
Dr Quay has served as CEO, president and chairman since the firm was incorporated in April 2009. Before joining Atossa, Dr Quay was chairman, president and CEO of MDRNA (now Marina Biotech), a biotechnology company focused on the development and commercialization of RNAi-based therapeutic products, from 2000 through 2008. Dr Quay is certified in anatomic pathology with the American Board of Pathology, completed both an internship and residency in anatomic pathology at Massachusetts General Hospital, and is a former faculty member of the Department of Pathology, Stanford University School of Medicine. Dr Quay is a named inventor on 76 US patents. He received an MD in 1977 and a PhD in 1975 from the University of Michigan Medical School. He also received his BA degree in biology, chemistry and mathematics from Western Michigan University in 1971.	Mr Guse has served as chief financial officer, general counsel and secretary since January 2013. His experience includes more than 20 years of counselling life sciences and other rapid growth companies through all aspects of finance, corporate governance, securities laws and commercialization. Mr Guse has practiced law at several international law firms, including from January 2012 through January 2013 as a partner at Baker Botts LLP, and from October 2007 to January 2012 as a partner at McDermott Will & Emery LLP. Mr Guse began his career as an accountant at Deloitte &Touche and is a licensed Certified Public Accountant in the state of California. Mr Guse earned a BS in business administration, an MBA from California State University, Sacramento, and a JD from Santa Clara University School of Law.
Vice president, regulatory affairs and quality: Janet Rose Rea	
Ms Rea has nearly 35 years of industry leadership experience in regulatory affairs and quality. She obtained her BS degree in microbiology from the University of Washington and was conferred a master's of science of public health from the same institution. Her career in the healthcare industry started with Miami, FL-based Dade Division of the American Hospital Supply Corporation (now Baxter), followed by Genetic Systems, and Immunex Corporation. She held positions with MDS Pharma, Targeted Genetics, and executive positions with AVI BioPharma (now Sarepta), Poniard Pharmaceuticals and Protein Sciences Corporation (Meriden, CT) and Therapeutic Proteins International (Chicago, IL).	

Principal shareholders	(%)
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Intracoastal Capital LLC	2.9
Vanguard Group	0.6
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