EDISON

Threshold Pharmaceuticals

Initiation of coverage

On the threshold of a blockbuster opportunity

Pharma & biotech

Phase III data for evofosfamide (TH-302) in soft tissue sarcoma (STS) and pancreatic cancer are expected by early 2016. These two indications alone could lead to blockbuster sales with partner Merck KGaA. Our estimates suggest the current market cap is more than underpinned by the risk-adjusted potential in STS together with net cash. We value Threshold at $949m based on evofosfamide in STS and pancreatic cancer and in a number of further opportunities in other solid tumours and blood cancers.

Year end	Revenue ($m)	PBT* ($m)	EPS* ($)	DPS ($)	P/E (x)	Yield (%)
12/13	12.5	(28.2)	(0.49)	0.0	N/A	N/A
12/14	14.7	(21.8)	(0.36)	0.0	N/A	N/A
12/15e	14.7	(32.1)	(0.47)	0.0	N/A	N/A
12/16e	14.7	(30.8)	(0.40)	0.0	N/A	N/A

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

Lead indications could have blockbuster potential

Phase III evofosfamide trials are ongoing in STS and pancreatic cancer. A planned interim efficacy analysis was recently completed in STS with the trial continuing as planned; overall survival (OS) data are expected by early 2016. Recruitment into the Phase III MAESTRO trial in advanced pancreatic cancer was recently completed and data are also expected by early 2016. STS and pancreatic cancer each represent blockbuster market opportunities for evofosfamide.

Other indications broaden evofosfamide's potential

A large Phase II trial in advanced non-squamous non-small cell lung cancer (NSCLC) was recently initiated and could potentially be sufficient for registration. Earlier-stage development is ongoing in recurrent glioblastoma and in relapsed/ refractory multiple myeloma, both potentially eligible for accelerated approval.

Evofosfamide's profile attracted partner Merck KGaA

Evofosfamide is a prodrug designed to be activated under conditions of low oxygen (hypoxia). Under these conditions a cytotoxic alkylating agent is released, selectively targeting these hypoxic regions, which are commonly found in solid tumours and can lead to resistance to traditional chemo- and radiotherapy. A $550m deal with Merck KGaA was signed in 2012; $110m in upfront and milestones have been received. Threshold is entitled to double-digit royalties on sales.

Valuation: Risk-adjusted NPV of $949m or $13.4/share

Our Threshold valuation is $949m or $13.4/share based on an NPV analysis, including net cash and evofosfamide in a variety of indications, risk-adjusted to reflect the current stage of development. This includes our base-case market share assumptions until there is more clarity on the magnitude of evofosfamide's benefit. Pro forma $86.8m net cash, post the $30m fund raise, should be sufficient to fund operations into 2017, beyond Phase III data readouts.

11 March 2015

Price	**US$4.47**
Market cap	**US$319m**

Net cash ($m) at end December 2014	58.6
Pro forma shares in issue	71.1m
Free float	86%
Code	THLD
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance

%	1m	3m	12m
Abs	22.1	38.0	(11.0)
Rel (local)	23.6	36.7	(18.2)

52-week high/low	US$5.12	US$2.70

Business description

Threshold Pharmaceuticals is a US oncology company focused on tumour hypoxia, a low-oxygen condition found in most solid tumours and some blood cancers. Evofosfamide is in Phase III for STS and pancreatic cancer and earlier trials in multiple other cancers, and is partnered with Merck KGaA.

Next events

Start of Phase II GBM trial	H115
Interim r/r MM Phase I/II data	Mid-2015
STS Phase III data	Q116
Pancreatic cancer Phase III data	Q116

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Investment summary

Company description: Breath of fresh air in oncology

Threshold is a US oncology company focused on developing therapeutic options that target tumour hypoxia, a low-oxygen condition that is found in most solid tumours, which can cause resistance to traditional chemotherapy and radiotherapy. Lead product evofosfamide is a prodrug that releases a DNA alkylator under conditions of low oxygen. It is currently in Phase III trials in both soft tissue sarcoma (STS) and in pancreatic cancer. In addition a Phase II study is underway in lung cancer, which could potentially be sufficient for registration. Evofosfamide is partnered with Merck KGaA in a deal worth up to $550m in milestones in addition to royalties. Threshold has also acquired a hypoxia imaging agent HX4 in development to potentially select evofosfamide responders and recently in-licensed TH-4000, a hypoxia-activated epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Threshold is based in South San Francisco, employs c 60 people and has raised c $263m in equity-based financings plus $110m in upfront and milestone payments to date.

Exhibit 1: Overview of Threshold's pipeline

Product	Indication	Setting	Stage	Comments
Evofosfamide	STS	First-line; combination with doxorubicin	Phase III	Top-line data by Q116; Phase II trial in Japan ongoing
	Pancreatic cancer	First-line; combination with gemcitabine	Phase III	Top-line data by Q116; Phase I trial in combination with Abraxane ongoing; Phase I trial in Japan ongoing
	Non-squamous NSCLC	Second-line; combination with Alimta	Phase II	Trial could be sufficient for registration; data in 2017
	Advanced melanoma	Monotherapy	Phase II	Collecting PET imaging and biomarker data
	GBM	Third-line; combination with Avastin	Phase I/II	IST Phase I/II nearing completion; FDA grant for Phase II to start 2015
	Multiple myeloma	Relapsed/refractory; combination with dexamethasone ± Velcade	Phase I/II	Velcade combination data presented at ASH; interim data expected at ASCO 2015; final data at ASH
	Solid tumours	Combination with anti-angiogenics	Phase I/II	Includes Phase I with Sutent; IST Phase I/II with Nexavar; IST Phase I with Votrient
	Advanced leukaemias	Monotherapy	Phase I	Trial complete demonstrating some CRs
[18F]-HX4	Hypoxia imaging agent for use in PET; in development for potential use with evofosfamide			Threshold acquired from Siemens in 2013
TH-4000	NSCLC	Mono, 2nd-line, EGFR+ve / T790M-ve	Phase I complete	In-licensed; planning to start a Phase II in H115

Source: Edison Investment Research. Note: STS: soft tissue sarcoma; NSCLC: non-small cell lung cancer; GBM: glioblastoma; PET: positron emission tomography; IST: investigator sponsored trial; CR: complete response.

Valuation: Risk-adjusted NPV of $949m or $13.4/share

Our Threshold valuation is $949m or $13.4/share, based on a risk-adjusted NPV analysis and including $86.8m pro forma net cash. Our valuation includes evofosfamide in STS, pancreatic cancer and NSCLC, in addition to some of the earlier stage opportunities. Our combined evofosfamide peak sales in 2024 of c $3.3bn include an average price in the US of $80k, which Threshold is targeting, and our base-case market share assumptions until there is more clarity on the magnitude of evofosfamide's benefit.

Sensitivities: Evofosfamide success or failure

The key sensitivity for Threshold relates to the success of evofosfamide, which is being developed in multiple oncology indications. Although this does introduce single-product risk, success or failure in one indication will not necessarily be an indicator of success or failure in another. Phase III data in the leading indications of STS and pancreatic cancer are expected by early 2016.

Financials: Cash beyond Phase III read-outs

Threshold had $58.6m in net cash at end Q414, which with $28.2m net from the fund raise should be sufficient to fund current operations into 2017, beyond both Phase III STS and pancreatic cancer data readouts. This cash runway could be extended through the receipt of additional milestone payments from partner Merck, although our forecasts do not include uncertain and unknown future milestones. Outstanding warrants could bring in c $100m (4m at $2.46 and 8.3m at $10.86).

Outlook: The threshold of a blockbuster opportunity

Threshold is approaching key value inflection points for its lead asset evofosfamide in the next 12-24 months, with Phase III data expected in both of the lead indications of STS and pancreatic cancer. Evofosfamide is targeting multiple indications in markets with multi-billion dollar opportunities, with the lead indications of STS and pancreatic cancer each having blockbuster potential, as do the later-stage indications of lung cancer, glioblastoma and multiple myeloma. Evofosfamide is partnered globally with Merck KGaA in a deal worth up to $550m in milestone payments, of which $110m has been received to date, in addition to royalties on global sales.

A simple approach to a common problem

Evofosfamide's mechanism of action is essentially based on the alkylating agent isophosphoramide mustard, a cytotoxic agent with similar properties to cyclophosphamide and ifosfamide. Evofosfamide is a prodrug, meaning it is inert until selectively activated under certain conditions, these being low oxygen, or hypoxia. Hypoxia is commonly associated with solid tumours and can lead to resistance to both traditional chemotherapy and radiotherapy, often leading to disease progression. Hence, evofosfamide could potentially be used to selectively target these often hard to treat tumours.

Data has been collected in over 1,500 patients to date demonstrating fairly consistent effects across a broad range of tumours, including blood cancers, either in combination therapy or alone; a summary of the later stage data is shown in Exhibit 2. As evofosfamide is a prodrug that is relatively inactive unless activated under hypoxic conditions, we would not expect significant systemic toxicity. The side effect profile observed to date has been manageable with dose-limiting mucositis/stomatitis and skin rash when used as monotherapy; in combination with other agents Grade 3/4 hematologic toxicities are not uncommon, although these are potentially from overlapping effects of the combination agent.

Exhibit 2: Overview of key evofosfamide data to date

Indication	Trial	PFS	OS	Evaluable	CR	PR	ORR	Comments
STS	Phase II	6.5 months	21.5 months	89	2	30	36%	No control arm; EORTC trial reported doxorubicin PFS 4.6 months and OS 12.8 months
Pancreatic cancer	Phase II	6.0 months*	9.2 months*	74*	2*	17*	26%	Control arm: PFS 3.6 months (p=0.008); OS 6.9 months (p=0.4)
NSCLC	Phase I/II	7.0 months	14.9 months	15	0	6	40%	No control arm; Alimta OS 9.3 months (FDA approved label)
GBM	Phase I/II	2.8 months	4.6 months	22	1	3	18%	Interim data to date
MM	Phase I/II	ND	ND	7	0	2	50%*	Interim data to date from the TBorD phase; 1 PR and 1 VGPR

Source: Edison Investment Research. Note: STS: soft tissue sarcoma; NSCLC: non-small cell lung cancer; GBM: glioblastoma; MM: multiple myeloma; PFS: progression free survival; OS: overall survival; CR: complete response; PR: partial response; ORR: objective response rate (OR + PR). *At the higher 340mg/m^2 dose.

With expertise in tumour hypoxia, Threshold also recently in-licensed TH-4000, a hypoxia-activated epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). Funds from the recent $30m capital increase will be used to support development of this asset, which we do not yet include in our valuation, and Phase II development in a NSCLC subset could start in the near term.

Evofosfamide's potential not reflected in share price

Despite numerous Phase III opportunities and following initial positive reception to both the Merck KGaA deal (the shares increased +132% when the deal was announced) and subsequent Phase IIb pancreatic cancer PFS data shortly after (+42%), Threshold's shares have since been negatively impacted by a number of external events, despite a generally surging US biotechnology sector (the Nasdaq Biotechnology Index is up 30% in the last year). These include the release of pancreatic cancer overall survival data, where the improvement was not statistically significant, the failure of late-stage competitor palifosfamide in STS and the approval of Abraxane in pancreatic cancer. We

believe concerns relating to these events may be misplaced, as described in more detail later in this report and believe the market is significantly undervaluing the potential for evofosfamide.

Our valuation suggests that the current share price is more than underpinned by our risk-adjusted valuation for STS and net cash alone, with all other indications and opportunities essentially free options at current levels.

Phase III soft tissue sarcoma data expected by Q116

Evofosfamide recently completed a planned interim efficacy analysis as part of the ongoing Phase III soft tissue sarcoma (STS) trial, which concluded that the trial should continue as planned. Overall survival data are expected shortly after the protocol-specified number of events (deaths) are reached, which the company expects to occur in H215. If positive, evofosfamide could be launched in 2017 with partner Merck KGaA. Evofosfamide is one of the most advanced front-line STS candidates in a market with c $1bn potential and limited competition.

21.5 month survival in Phase II

In an open-label Phase II study of 300mg/m^2 of evofosfamide in combination with doxorubicin as front-line therapy in 91 STS patients, overall survival (OS) was 21.5 months and progression- free survival (PFS) was 6.5 months; there was no comparator arm in the trial. A European study[1] (EORTC 62012) reported survival of 12.8 months in doxorubicin treated STS patients and PFS of 4.6 months. While not directly comparable, the EORTC data does provide an indication of the potential magnitude of evofosfamide's benefit versus doxorubicin, which is the comparator arm in the ongoing Phase III trial. There were two complete responses (CR) and 30 partial responses (PR) for an overall response rate (ORR) of 36%. Detailed data were recently published.[2]

48 patients (53%) who had not progressed after six cycles of evofosfamide/doxorubicin combination therapy (induction) elected to continue on single-agent evofosfamide maintenance therapy. Tumour response improvements were observed: five patients with stable disease (SD) improved to a PR and one PR improved to a CR.

Nausea and fatigue were the most common adverse events (AEs) during induction. The most common Grade 3/4 AEs were hematologic, with 31% neutropenia, 32% thrombocytopenia and 36% anaemia. According to the EORTC 62012 trial, single-agent doxorubicin was associated with 37% neutropenia, <1% thrombocytopenia and 4% anaemia. Grade 3/4 hematologic toxicity was far less frequent during maintenance with monotherapy evofosfamide.

Phase III ongoing with data by Q116

Threshold started a Phase III trial of evofosfamide in STS in September 2011 in partnership with SARC (Sarcoma Alliance for Research through Collaboration). The trial is investigating 300mg/m^2 evofosfamide in combination with doxorubicin versus doxorubicin alone in 640 STS patients (locally advanced unresectable and metastatic disease). Recruitment was completed in December 2013. The trial design has been agreed with the FDA under a Special Protocol Assessment (SPA), meaning the design of the trial is acceptable for approval. Unlike Votrient (pazopanib, GSK), which was approved in 2012 for second-line STS based on PFS, Threshold's trial is based on OS, a gold standard endpoint in cancer trials. The trial is designed to demonstrate a 33% decrease in the death hazard ratio (or HR=0.75), which equates to a four-month OS benefit and assumes a 12-month control arm survival. Threshold believes an OS improvement equal to or greater than 21% would be sufficient for approval.

1 Judson I *et al*. The Lancet Oncology - 1 April 2014 (Vol. 15, Issue 4, Pages 415-423).
2 Chawla, S.P. *et al*. Journal of Clinical Oncology 32, 3299–3306.

Trial continues as planned following planned interim analysis

A planned interim efficacy and safety analysis was recently completed based on 256 deaths, which concluded that the trial should continue as planned. The trial could have been stopped early if evofosfamide demonstrated sufficient benefit to clearly establish efficacy, which was defined as around a 45% OS improvement. Although no formal futility analysis was included, the IDMC could have stopped the trial early if evofosfamide was unlikely to meet the trial's primary endpoint.

Current event rate suggests OS data by Q116

Based on the current event rate, Threshold expects that the number of events (n=434 deaths) for the primary analysis will be reached in H215, allowing for top-line data to be made available shortly thereafter. This is slightly later than the previous expectation of mid-2015. Timelines for event-driven trials can be difficult to predict and while a longer time to reach the number of events indicates that some patients in the trial are surviving for longer than expected, it is impossible to conclude which patients. If survival in the doxorubicin arm is around 17 months (an unexpected observation in the doxorubicin control arm of the Phase III trial of palifosfamide), evofosfamide could still hit the primary endpoint if OS is around 20.6 months, slightly less than the 21.5 months reported in the previous Phase II trial. We note that more recently the doxorubicin control arm in CytRx's Phase II frontline STS trial reported OS of 14.4 months, closer to Threshold's control arm assumption.

Evofosfamide could launch mid-17 in a $1.4bn STS opportunity

The American Cancer Society estimates there were around 12,020 new cases of STS diagnosed in the US in 2014. In Europe it has been estimated that there are around 27,908 new cases of sarcoma per year in the EU27, of which 84% are STS.[3] Of these 35k new STS patients each year, it is estimated that around 40-60% have unresectable or metastatic disease,[4] the patient population enrolled in the ongoing Phase III trial. This leads us to a target evofosfamide market of 18k patients.

There are currently limited treatment options for front-line STS, with current standard-of-care with doxorubicin. We estimate doxorubicin is used in most, if not all advanced/metastatic STS patients. Threshold is targeting evofosfamide pricing of around $80k per patient per year, in line with the median price of recently approved oncology products. Hence, based on the target patient market, this suggests a potential evofosfamide market opportunity of around $1.4bn. We forecast launch from mid-2017, assuming data by Q116, filing by mid-2016 and assuming priority review is awarded (which was recently granted to Yondelis for second-line STS).

Evofosfamide is the most advanced first-line STS candidate

To our knowledge, evofosfamide is the most advanced pipeline candidate in development for first-line treatment of advanced STS. This follows the failure of palifosfamide in the Phase III PICASSO 3 trial in metastatic front-line STS in 2013 (which failed owing to a lack of PFS benefit compared to doxorubicin). The next most-advanced front-line treatment in development is aldoxorubicin, which has reported top-line data from a Phase IIb trial in first-line STS and is also in a Phase III trial in second-line STS. On a recent conference call, CytRx stated that it did not currently plan to pursue further studies in frontline STS. Aldoxorubicin if approved is likely to replace doxorubicin and therefore the combination of evofosfamide with aldoxorubicin could still have utility in treating STS if this combination is found to offer patient benefits; hence we do not see aldoxorubicin as a direct competitor to evofosfamide. GSK's Votrient (pazopanib) is approved for second-line treatment, as is Zeltia's Yondelis (trabectedin) in Europe.

[3] Stiller C A *et al*. Eur J Cancer. 2013 February; 49(3): 684–695.
[4] Morgan S.S. *et al*. Clinical Sarcoma Research 2014. 4:2-5.

Exhibit 3: Overview of late-stage STS development

Product	Company	Setting	Status	Key data to date	Comments
Evofosfamide	Threshold	1st line; combo with dox	Phase III	Phase II: PFS 6.7 months; OS 21.5 months	Top-line data by Q116
Aldoxorubicin	CytRx	1st line; mono	Phase IIb	Phase IIb: PFS 8.4 months; OS 16.0 months	Now develop for 2nd line
Trabectedin	Zeltia/JNJ	2nd line; mono; L-sarcoma	Approved EU; Phase III US	EU trial: PFS 3.7 months; OS 13.9 months	NDA filed Dec 2014
Aldoxorubicin	CytRx	2nd line; mono	Phase III	Phase Ib/II: PFS 6.4 months; OS 16 months	PFS data mid-2016
Eribulin	Eisai	2nd line; mono; L-sarcoma	Phase III	Phase II L-sarcoma: 31.6% PFS at 12 wks	Data in 2015

Source: Edison Investment Research. Note: dox=doxorubicin; mono=monotherapy; L-sarcoma= liposarcoma or leiomyosarcoma

Phase III pancreatic cancer data by early 2016

Recruitment into the Phase III trial of evofosfamide as first-line treatment in advanced pancreatic cancer was recently completed by partner Merck KGaA and data are expected by early 2016. If positive, these could allow for first launches from 2017. Evofosfamide has already demonstrated a significant PFS improvement in a Phase II trial. OS was one of several secondary endpoints, and the trial was not powered to detect an OS improvement; the analysis was also confounded by the crossover design. Nevertheless, OS of 9.2 months would represent an improvement over most treatments.

Significant PFS benefit but OS confounded by crossover

Evofosfamide was previously investigated in an open-label Phase II study in 214 pancreatic cancer patients, which included two doses of evofosfamide (240mg/m^2 and 340mg/m^2) in combination with gemcitabine versus gemcitabine alone. The primary endpoint of the trial was PFS, with both doses demonstrating a significant improvement compared to gemcitabine alone. The higher evofosfamide dose reported PFS of six months, compared to 3.6 months with gemcitabine (HR=0.59, p=0.008).

OS was a secondary endpoint and the higher dose of evofosfamide reported OS of 9.2 months compared to 6.9 months with gemcitabine. This was not a significant difference, with a HR of 0.86 (p=0.39). The trial was not powered to detect an OS difference and in addition included a crossover design that allowed patients who had progressed on gemcitabine to receive evofosfamide. Hence, OS in the gemcitabine group may have been improved by the 26 patients (of 69 patients) who did go on to receive evofosfamide. The study authors in the Journal of Clinical Oncology article concluded that both the trial size and the crossover could explain the lack of significant difference in OS across treatment arms. All other secondary endpoints, including six- and 12-month OS rates, met statistical significance.

Rash and stomatitis (inflammation inside the mouth ie ulcers) were more common AEs in evofosfamide treated patients; in terms of Grade 3/4 AEs at the higher 340mg/m^2 dose there was 3% Grade 3 rash and no Grade 3/4 stomatitis. At the higher evofosfamide dose there was 55% Grade 3/4 thrombocytopenia and 43% Grade 3/4 neutropenia, compared to 12% and 17% with gemcitabine, respectively. There was no difference in discontinuation owing to AEs with 14% on the higher evofosfamide dose and 19% on gemcitabine.

Phase III data expected by early 2016, forecast launch in 2017

Partner Merck KGaA started the pivotal Phase III MAESTRO trial (**m**etast**a**tic or unr**es**ectable pancrea**t**ic adenocar**c**in**o**ma) in January 2013; Merck is responsible for conducting the trial. The trial is investigating 340mg/m^2 of evofosfamide in combination with gemcitabine versus gemcitabine alone in 660 patients with pancreatic cancer (first-line, locally advanced unresectable or metastatic disease). Recruitment was completed in November 2014. The primary endpoint of the trial is OS and secondary endpoints include PFS and ORR.

Threshold and Merck currently expect top-line data from the trial could become available shortly after the protocol-specified number of events (deaths) are reached, which is expected to occur in H215. If positive, allowing time for filing followed by a standard one year for regulatory review, approval and launch are possible in 2017. The trial design has been agreed with the FDA under a Special Protocol Assessment (SPA), meaning the design of the trial is acceptable for approval; this could be important, given Abraxane has been approved since the MAESTRO trial was initiated, helping to reduce the risk that the FDA asks for a trial of evofosfamide either in combination or compared to Abraxane prior to approval. We note that a Phase I combination trial with evofosfamide/Abraxane/gemcitabine is already underway.

Pancreatic cancer could be a significant opportunity

The American Cancer Society estimates there were 46,420 new cases of pancreatic cancer diagnosed in the US in 2014. In the five major European markets the annual incidence is estimated at 51,402. Of the newly diagnosed patients, around 30% are locally advanced and around 50% are metastatic[5] (pancreatic cancer is generally difficult to diagnose early and is typically asymptomatic until it has already spread), suggesting a target patient population of around 78k.

Current standard of care treatment for advanced pancreatic cancer is with gemcitabine (and often with gemcitabine containing regimens), although both FOLFORINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin) and more recently the combination of gemcitabine with Abraxane (nab-paclitaxel, Celgene), which was approved October 2013 for pancreatic cancer, have shown survival benefits (Exhibit 4) compared to gemcitabine alone. Use of FOLFORINOX is limited to use in patients with a good performance status, owing to a less favourable safety profile than gemcitabine.

Exhibit 4: Survival data of the main products used to treat pancreatic cancer

Product	Company	Treatment	Median OS
Gemzar (gemcitabine)	Eli Lilly	Monotherapy	5.7 months versus 4.2 months fluorouracil
Tarceva (erlotinib)	Roche (Genentech)/Astellas	Combination with gemcitabine	6.4 months versus 6.0 months gemcitabine
Abraxane (nab-paclitaxel)	Celgene	Combination with gemcitabine	8.5 months versus 6.7 months gemcitabine
FOLFORINOX	Generic	Monotherapy	11.1 months versus 6.8 months gemcitabine

Source: Edison Investment Research. OS data from the FDA approved label, where available. Note: Sutent (sunitinib) is excluded from this table as it is approved for a rare pancreatic cancer.

Although dosing in pancreatic cancer is higher than in STS (340mg/m^2 on days 1, 8 and 15 versus 300mg/m^2 on days 1 and 8 in STS) and each cycle is longer (28 days versus 21 days in STS), we maintain pricing at Threshold's targeted $80k per patient per year. Assuming that gemcitabine is used in most advanced/metastatic patients suggests a market opportunity of $7bn. Abraxane, priced at $6-8kper month, already commands a >40% share of newly diagnosed US patients ie 50% of advanced/metastatic patients, leaving a pancreatic cancer market opportunity for evofosfamide of around $3.5bn. If evofosfamide can take share from Abraxane, or if the combination of evofosfamide with Abraxane and gemcitabine, which is being investigated in an ongoing Phase I study, is found to meaningfully improve survival, this could expand the market opportunity.

Competitive landscape in pancreatic cancer

Pancreatic cancer remains one of the most resistant cancers to traditional therapies (surgery, radiotherapy, chemotherapy) and patients with advanced disease have a five-year survival rate of less than 5%. Abraxane was recently approved based on a 1.8-month survival improvement, which although modest is considered clinically relevant, highlighting the poor prognosis of these patients. However, there have also been a number of clinical trial failures including Onconova's rigosertib and Amgen's ganitumab, both of which failed in Phase III trials, highlighting the difficulty in treating this disease. AB Science's masitinib failed to show a survival benefit in its Phase III trial and then

[5] Malik NK *et al*. Journal of Gastrointestinal Oncology 2012;3(4):326-334.

failed to gain conditional European approval based on a reported benefit in certain subsets; a further Phase III trial in these patients will need to be conducted prior to potential approval.

There remain a number of products in late-stage clinical development (Exhibit 5), although many of these are for second and third-line treatment, placing evofosfamide as one of the most advanced in development for first-line treatment of advanced pancreatic cancer. We note there are some other candidates including NanoCarrier's NC-6004 in Phase III development for first-line pancreatic cancer, although trials are currently only ongoing in Asia.

Exhibit 5: Overview of late-stage pancreatic cancer development

Product	Company	Setting	Status	Key data to date	Comments
Evofosfamide	Merck KGaA/ Threshold	1st line; combo with gem	Phase III	Phase II: PFS 6 vs 6.9 months gem (p=0.008), OS 9.2 vs 6.9 months gem (p=0.8)	Expect data by early 2016
Masitinib	AB Science	1st line; combo with gem	Phase III (in planning)	Phase III: OS 7.7 vs 7.0 months gem (ns). Pain subset OS 8.1 vs 5.4 months gem Biomarker subset: OS 11.0 vs 5.0 months gem	Further trial being planned following EMA refusal to grant conditional approval
Algenpantucel-L	NewLink Genetics	1st line (borderline resectable, non-mets); combo with soc	Phase III (PILLAR)	Phase II (post-surgical resection): OS >35 months in high anti-CALR subset; OS 19.2 months in normal anti-CALR subset	Complete enrolment mid-15
		Post-surgery	Phase III (IMPRESS)		Second interim data in Q115
Glufosfamide	Eleison Pharmaceuticals	2nd line; mono	Phase III	Phase III: 18% OS improvement vs BSC (ns)	Threshold out-licensed glufosfamide in 2009
MM-398	Merrimack	2nd line; combo with 5-FU and leucovorin	Phase III	Phase III: OS 6.1 months vs 4.2 months with 5-FU	Trial completed in May 14; complete NDA filing by Q115
Ruxolitinib	Incyte	2nd line; combo with cap	Phase III (JANUS 1 and JANUS 2)	Phase II: OS 136.5 vs 129.5 days cap (p=0.25); High CRP subset OS 83 vs 55 days cap (p=0.01)	Two Phase III trials ongoing; data expected 2016
Y90-clivatuzumab tetraxetan	Immunomedics	3rd line; combo with gem	Phase III	Phase Ib: OS 4.0 months (combo with gem)	Expect to complete enrolment in mid-2015

Source: Edison Investment Research. Note: combo=combination therapy; mono=monotherapy; gem=gemcitabine; mets=metastatic; soc=standard-of-care; 5-FU=fluorouracil; PFS=progression free survival; OS=overall survival; BSC=best supportive care; ns=not significant; cap=capecitabine; EMA=European Medicines Agency; NDA: new drug application.

Potential registration trial started in lung cancer

Threshold recently started a large Phase II lung cancer trial, broadening evofosfamide's late-stage development opportunities. Given the size and design of the trial, we believe this could potentially be used as a registration study for evofosfamide in this indication. Data could be available in 2017, and if sufficient for approval, evofosfamide could potentially launch in lung cancer in 2018.

Previous data suggest potential survival benefits

There have been a number of earlier stage evofosfamide trials in solid tumours, and in particular the Phase I/II trial investigating evofosfamide in a variety of combinations in various solid tumours included a subset of NSCLC patients who received evofosfamide in combination with pemetrexed (Alimta). There were 18 non-squamous NSCLC (non-small cell lung cancer) second-line patients and evofosfamide demonstrated overall survival of 14.9 months and PFS of 7 months. There was no control arm in the trial but in the Alimta registration trial in second-line NSCLC versus docetaxel, a subset analysis in non-squamous patients demonstrated OS in the Alimta arm of 9.3 months compared to 8.0 months on docetaxel (data from the FDA approved Alimta label). Tumour responses from 15 evaluable patients included six (40%) PRs and six (40%) SD. Adverse events were similar to those observed in other trials, with the most common being fatigue, anaemia, stomatitis and nausea.

Ongoing trial could potentially be sufficient for registration

Threshold started a Phase II trial of evofosfamide in combination with pemetrexed versus pemetrexed alone in July 2014. The trial is investigating 400mg/m^2 of evofosfamide in 440 second-

line patients with advanced non-squamous NSCLC. The primary endpoint of the trial is OS, with secondary endpoints including PFS and ORR. Given the size and design of the trial, with an overall survival endpoint, we believe this could potentially be sufficient for registration, although this will likely be dependent on the quality of the data and the magnitude of benefit. Alimta was approved as second-line treatment in NSCLC based on a 571 patient trial.

Data from the trial could be available in 2017, and if we assume that it will be sufficient for registration then allowing a standard one-year regulatory review, evofosfamide could potentially be approved and launched in NSCLC in early 2018.

An evolving but significant market

The American Cancer Society estimates there were 224k new cases of lung cancer in the US in 2014. NSCLC is the most common type, affecting around 85%, with 70-75% non-squamous cell. The American Lung Association suggests that of these patients, nearly 60% are advanced disease suggesting around 76k advanced non-squamous NSCLC patients each year in the US. It is estimated that around 40-50%[6] of patients received second-line treatment. This suggests a target evofosfamide patient population in the US of c 30k, with similar in the major European countries.

Based on the patient population alone, the lung cancer market opportunity for evofosfamide could be approaching $5bn. However, lung cancer is a competitive market and there are a number of immuno-oncology compounds in late-stage development in various settings, including in the target market for evofosfamide. Hence, based on this more competitive environment and potentially changing treatment landscape the market potential is likely to be below this estimate.

Evofosfamide earlier-stage oncology programmes

Outside the three later-stage clinical programmes, evofosfamide is also being investigated in a number of other settings. These include in solid tumours in combination with anti-angiogenics, in blood cancers in combination with chemotherapy, and as monotherapy in certain cancers. A summary of Threshold's pipeline is shown in Exhibit 1.

Glioblastoma (GBM) Phase II plans confirmed

Evofosfamide is currently in a Phase I/II investigator-sponsored trial in combination with Avastin (bevacizumab) as third-line treatment in recurrent GBM patients who have progressed following second-line Avastin treatment. Typical treatment for newly diagnosed GBM patients after surgical resection is with temozolomide and radiotherapy; Avastin is approved in the US for second-line treatment but once Avastin fails there remain limited treatment options and patients have a poor prognosis. A further third-line Avastin-based regimen has shown PFS of 38 days and OS of 82 days.[7]

In the evofosfamide Phase I/II trial, the first three patient cohorts were administered evofosfamide pre-operatively (to determine the ability of evofosfamide to penetrate the blood brain barrier) who then went on to receive escalating doses of evofosfamide in combination with Avastin. The surgical component of the trial was removed, allowing patients to move directly to the combination without the need for surgery. The trial has completed enrolment of the planned 28 patients and data from the 23 patients who received the combination of evofosfamide with Avastin were recently presented at the SNO conference (Society for Neuro-Oncology).

OS data as reported at SNO 2014 is 4.6 months and PFS is 2.8 months. There is one CR and three PRs, for an 18% ORR in the 22 evaluable patients. 10 patients have SD and one patient who had

[6] Stinchcombe TE and Socinski MA. The Oncologist January 2008 vol. 13 Supplement 1 28-36.
[7] Quant EC *et al*. Neuro-Oncology 2009;11:550-555.

PR as a best response has had SD of nearly 45 months. There have been no Grade 4 AEs and only three Grade 3 AEs. The majority of AEs were Grade 1 or 2 mucosal-related, which were not dose-limiting. The recommended Phase II dose has been established as 670mg/m^2 in combination with Avastin. This is higher than the MTD established in other combination trials of evofosfamide in STS, pancreatic and lung cancer and could be due to fewer overlapping toxicities with Avastin in addition to less frequent, every other week, dosing.

The lead investigator from the ongoing Phase I/II study has been awarded an FDA grant to pursue a Phase II study. This planned trial will be in the same patient setting and will recruit up to 33 patients at the MTD. The FDA granted accelerated approval to Avastin for second-line GBM based on the objective response rate in two Phase II single-arm trials. Hence, it is possible that the planned Phase II trial of evofosfamide could form a key part of an NDA. We conservatively assume that a further trial will be needed to secure approval and forecast potential launch in 2020. There are around 14-15k new cases of GBM in the US each year and we assume that around 40% of these patients could be eligible for third-line therapy, which gives a potential market opportunity for evofosfamide of $540m as third-line treatment. There could be upside to this if development is moved into earlier treatment settings, including as front-line treatment in combination with radiotherapy, a combination that Threshold is currently considering for development.

Dosing established for future development in multiple myeloma

Threshold and partner Merck are currently conducting a Phase I/II trial of evofosfamide in combination with dexamethasone with or without Velcade (bortezomib) in relapsed/refractory multiple myeloma (r/r MM). This is a three-part study consisting of: (1) a dose escalation phase in combination with dexamethasone; (2) dose expansion in combination with dexamethasone; and (3) evofosfamide combined with low-dose dexamethasone with or without Velcade (bortezomib), the TBorD part (TBorD: **T**H-302, **bor**tezomib, **d**examethasone). 18 patients of a planned 24 have been recruited into this TBorD phase and initial data from nine patients were recently presented at ASH. We expect further interim data to potentially be available at ASCO 2015, with final data at ASH.

Evofosfamide Phase II dosing was established as 340mg/m^2 in combination with dexamethasone and Velcade. In data from seven evaluable patients there was one very good partial response (VGPR) and one PR, both at the recommended Phase II dose. Safety data from eight patients were available, with the most common AEs thrombocytopenia, anaemia and fatigue. There was 50% Grade 3/4 thrombocytopenia. Previous data from the dose escalation and expansion phases in 24 patients treated with the MTD of 340mg/m^2 in combination with dexamethasone demonstrated three PRs (out of 23 evaluable patients) and two patients had a minimal response (MR).

Based on these data, we expect Threshold to move forwards to Phase II in r/r MM. Both Kyprolis (carfilzomib) and Pomalyst (pomalidomide) were granted accelerated approved in the US based on the objective response (ORR) in Phase II trials in around 200 r/r MM patients, hence evofosfamide approval could be possible based on a similar trial design and scope (monotherapy Kyprolis failed recently to improve overall survival in the Phase III FOCUS trial in r/r MM but did show a PFS benefit in the Phase III ASPIRE three-drug combination trial). Assuming this trial could start in 2016 and allowing two to three years to complete, evofosfamide could potentially be approved in 2020. In the US alone there are around 24k new cases of multiple myeloma and combined 2014 US sales of carfilzomib and pomalidomide are c $750m, highlighting the potential opportunity in this indication. The c $1.3bn opportunity for evofosfamide in r/r MM could be expanded if development is moved into earlier treatment settings.

Combination with anti-angiogenics in various solid tumours

Anti-angiogenics inhibit the formation of new blood vessels. They have found particular utility as a treatment for cancer owing to the necessity of a blood supply for tumour growth; one of the first approved anti-angiogenics was Avastin (bevacizumab), a VEGF inhibitor. Preventing the formation of nutrient supplying blood vessels to tumours could potentially lead to hypoxic (low oxygen) areas within the tumours; this is supported by preclinical data suggesting anti-angiogenics can induce tumour hypoxia, the conditions under which evofosfamide is activated. Hence, the combination of evofosfamide with an anti-angiogenic could present an attractive therapeutic option, and evofosfamide is already in an investigator sponsored study in combination with Avastin for the treatment of GBM. Other studies investigating this combination include:

- **In combination with Sutent (sunitinib):** Threshold has completed enrolment into a Phase I dose escalation trial of evofosfamide in combination with Sutent in renal cell carcinoma (RCC), gastrointestinal stromal tumour (GIST) and pancreatic neuroendocrine tumours (PNET). Some interim data have been made available with one PR in GIST (out of four evaluable GIST patients) and three PRs in RCC (out of eight evaluable RCC patients).
- **In combination with Nexavar (sorafenib):** An investigator sponsored Phase I/II trial of evofosfamide in combination with Nexavar in advanced, unresectable RCC and HCC (hepatocellular carcinoma) is ongoing.
- **In combination with Votrient (pazopanib):** An investigator sponsored Phase I trial of evofosfamide in combination with Votrient in advanced solid tumours has completed and data were presented at AACR (American Association for Cancer Research) in 2013 (12% PR and 64% SD).

Monotherapy in advanced leukaemias

Given the low oxygen environment within the bone marrow, a hypoxia-activated therapy could have a potential role in treating various blood cancers. This has already been evidenced with the ongoing Phase I/II multiple myeloma trial. In addition, a Phase I monotherapy trial in advanced leukaemias has completed demonstrating some complete responses. We do not currently include any contribution for evofosfamide outside of multiple myeloma in our model and valuation.

Advanced melanoma trial assessing biomarkers

Evofosfamide is currently in a Phase II trial as monotherapy in 40 patients with advanced melanoma. One of the main aims of the trial is to assess potential biomarkers and PET imaging that can help predict responders. This trial started in August 2013 following previous data in a Phase I/II trial investigating evofosfamide in a variety of solid tumours, which included a subset of 34 melanoma patients. In these patients there were seven PRs and 12 SD for an ORR of 56%. PFS was 3.5 months. Data from this trial could become available in 2015.

As this is predominantly a biomarker study, we do not include the potential for evofosfamide in advanced melanoma in our valuation. In addition, this is an indication where there have been a number of recent advances and approvals, particularly checkpoint inhibitors (eg CTLA-4, PD-1, PDL-1), which help to enhance the immune system response to fight cancer. In addition treatment with targeted therapies such as BRAF and MEK inhibitors are transforming treatment strategies. Hence if evofosfamide is to have a role in melanoma, it seems likely that a combination approach with these newer treatments will be key.

Background to evofosfamide and tumour hypoxia

Evofosfamide is a prodrug that is activated in areas of low oxygen (hypoxia). Under these conditions a DNA alkylating agent (bromo isophosphoramide) is released that can more selectively target these regions. This can reduce systemic side effects associated with less-specific alkylators, in addition to targeting these areas, which are typically harder to treat with standard chemo- and radiotherapy. Evofosfamide has been awarded orphan drug status for both STS and pancreatic cancer in the US and Europe and was recently awarded FDA Fast Track status in STS. Evofosfamide is patent protected until 2027-30 (excluding extensions).

Tumour hypoxia

Hypoxia is common in solid tumours owing to both rapid tumour growth and abnormal blood vessel formation leading to regions with limited oxygen within the tumour. These areas are associated with resistance to traditional cancer treatment; for chemotherapy that targets rapidly dividing cells, these regions present a challenge owing to slower division due to the lack of oxygen. In addition, mutations resulting as a consequence of these low oxygen areas can allow tumour cell survival in inhospitable environments, which can lead to progression and tumour spread (metastasis).

DNA-alkylating prodrug

Evofosfamide is a prodrug which is inert under normal oxygen levels, but is activated under hypoxic conditions. Upon activation it releases Br-IPM (bromo isophosphoramide), a DNA alkylating agent. Alkylators damage DNA, leading to prevention of DNA replication, division and transcription and are commonly used to treat cancer.

Evofosfamide Merck KGaA deal

In February 2012 Threshold signed a partnering agreement with Merck KGaA for evofosfamide. Under the terms of deal Threshold is entitled to receive up to $550m in milestone payments in addition to royalties. The deal includes co-development rights in addition to various commercialisation options.

- **$550m in milestone payments:** Threshold received a $25m upfront payment upon execution of the deal and to date has received $110m in total. $100m of development milestones remain (we assume the majority of these are linked to STS and pancreatic cancer regulatory approvals) in addition to $340m of commercial milestones, which we assume are sales-related.
- **Co-development terms:** Worldwide development costs of evofosfamide are shared with Merck KGaA paying for 70%. Although costs are shared, Threshold has primary responsibility for evofosfamide in STS in the US, conducting the ongoing Phase III trial and the NDA submission.
- **Royalty rate:** Merck KGaA has exclusive global commercialisation rights with Threshold entitled to receive a tiered double-digit royalty on sales. When the deal was signed the STS Phase III trial was already ongoing and the Phase IIb pancreatic trial was close to completion (positive PFS data were announced two weeks later). With a development cost-share agreement, we assume the tiered double-digit royalty rates starts in the teens.
- **Commercialisation terms:** Threshold has an option to co-promote evofosfamide in the US. Threshold also has the option to co-commercialise evofosfamide in the US under certain conditions in exchange for a profit share of up to 50%.

Sensitivities

Threshold is subject to the usual biotech and drug development risks, including clinical development delays or failures, regulatory risks, competitor successes, partnering setbacks, and financing and commercial risks. The key sensitivity for Threshold relates to the success of evofosfamide, which is being developed in multiple oncology indications. Although this does introduce single-product risk, success or failure in one indication will not necessarily be an indicator of success or failure in another.

Phase III data in the lead indications of STS and prostate cancer are expected in 2016. Both Phase III trials have been agreed with the FDA under an SPA. This does not guarantee approval even if the trial is positive, but does provide comfort that the design is sufficient to make an efficacy claim.

Evofosfamide is partnered globally with Merck KGaA with development costs shared and Merck initially responsible for commercialisation. This removes commercial execution risk as Merck KGaA is an established oncology player with products including blockbuster Erbitux for colorectal cancer and head and neck cancer, which generated sales of €904m ($1.2bn) in 2013. A joint steering committee consisting of representatives from both Threshold and Merck KGaA has been established to agree future development of evofosfamide; despite this, Threshold likely has limited ability to expedite development if progress is stalled; likewise Threshold's commitment to fund 30% of development costs may put a strain on financial resources if significant development is planned.

Valuation

Our Threshold valuation is $949m or $13.4/share, based on a risk-adjusted NPV analysis, which includes $86.8m pro forma net cash. The breakdown of our rNPV base-case valuation, which uses a 12.5% discount rate, is shown in Exhibit 6. Our valuation includes evofosfamide in the later-stage indications of STS, pancreatic cancer and NSCLC, in addition to an indicative value for some of the earlier stage opportunities. For each indication, we include our forecasts for the development spend needed to obtain regulatory approval, to which Threshold contributes 30% as per the terms of the deal with Merck KGaA. We also include our sales forecasts, which include average US pricing of c $80k per patient per year, which Threshold is targeting in all indications, and using conservative base-case assumptions for market penetration rates, on which Threshold will earn a tiered double-digit royalty under the deal with Merck KGaA; we assume in the teens. We do not include any CoGS or sales and marketing spend, as we assume these will be covered by Merck for all indications in all regions, even if Threshold does opt to co-promote. Our valuation does not currently include any contribution for TH-4000.

Key peak sales assumptions

As described earlier in the report, we have estimated the potential market opportunity for evofosfamide in each indication based on an average price of c $80k per patient per annum, which Threshold is targeting, and the number of patients that could be eligible for treatment with evofosfamide. However, until the magnitude of evofosfamide's benefit is reported in the Phase III trials, and market dynamics at the time of launch are better understood, we use base-case market share assumptions to arrive at peak sales forecasts for the purposes of our valuation.

In STS we assume evofosfamide could be used in around 50% of all advanced/metastatic patients, leading to peak sales of $710m. Our penetration rate could prove conservative as we believe that ifosfamide is used fairly extensively in combination with doxorubicin to treat STS, despite a lack of OS benefit coupled with increased side effects. In pancreatic cancer, the most recently approved product Abraxane has captured a 40% share of newly diagnosed patients. If we assume that

evofosfamide could capture 40% of the remaining market of advanced/metastatic patients, leaving room for either increased competition or for Abraxane to take more market share, we arrive at peak sales of $1.4bn. In lung cancer we conservatively apply a 15% penetration, given the rapidly evolving treatment landscape and in GBM and r/r MM we apply 20-30% penetration as indicative valuations.

Exhibit 6: Threshold rNPV base-case valuation

Product	Indication (US and Europe)	Launch	Market opportunity	Base-case penetration	Peak sales ($m)	Value ($m)	Probability	rNPV ($m)	NPV/share ($/share)
Evofosfamide	STS	2017	$1.4bn	50%	710	404.9	60%	238.9	3.4
	Pancreatic Cancer	2017	$3.5bn	40%	1,400	932.4	50%	459.8	6.5
	NSCLC	2018	$5.0bn	15%	740	318.9	40%	122.0	1.7
	GBM	2020	$540m	30%	160	55.9	30%	16.1	0.2
	r/r MM	2020	$1.3bn	20%	260	88.9	30%	24.9	0.4
Net cash/(debt)						86.8	100%	86.8	1.2
Valuation						**1,887.7**		**948.6**	**13.4**

Source: Edison Investment Research

For STS we apply a 60% probability of success, which is fairly typical for a product in Phase III. In pancreatic cancer we assign a more conservative 50% as this is a hard to treat indication. There is more limited data in NSCLC and this is currently in a Phase II trial, so our probability of success is 40%. For GBM and r/r MM, both at earlier stages of development, we assign a 30% probability.

Evofosfamide's pricing, penetration and hence peak sales will ultimately depend on the magnitude of benefit in clinical trials. Exhibits 7 and 8 highlight the potential impact to our non-risk adjusted NPV and our rNPV based on our currently assumed risk adjustments based on a range of peak sales in 2024. If Threshold opts to co-commercialise in the US in exchange for a profit share up to 50:50, this could provide upside to our valuation, essentially equating to a higher average margin on evofosfamide than the assumed tiered double-digit royalty. Exhibits 7 and 8 also present a range of average net margins/royalty rates on our NPV and rNPV.

Exhibit 7: Threshold NPV based on evofosfamide peak sales in 2024 and average margin/royalty

	$500m	$1000m	$2000m	$3300m	$4000m	$5000m
15%	319	550	1010	1521	1797	2174
18%	358	638	1215	**1888**	2257	2763
25%	441	792	1495	2312	2767	3385
30%	501	913	1737	2708	3251	3991

Source: Edison Investment Research. Note: This assumes all indications are included with 100% probability of success.

Exhibit 8: Threshold rNPV based on evofosfamide peak sales in 2024 and average margin/royalty

	$500m	$1000m	$2000m	$3300m	$4000m	$5000m
15%	197	309	533	781	915	1098
18%	216	352	633	**949**	1138	1383
25%	256	427	768	1165	1385	1685
30%	285	485	886	1357	1620	1978

Source: Edison Investment Research. Note: The rNPV is based on the current probabilities we apply to the various indications.

Financials

Threshold reported total revenue of $14.7m in 2014, which consists entirely of deferred revenue from milestones already received under the deal with Merck KGaA; to date $110m of the total $550m in milestones has been received. We do not include unknown or uncertain milestones in our forecasts, hence our revenue projections are flat in future years with continued deferred revenue recognition.

R&D spend in 2014 was $35.8m of which we assume the majority was for 30% of evofosfamide worldwide development costs; G&A was $10.1m. Our forecasts include a similar level of spend in coming quarters and years although R&D could increase with the start of additional trials beyond those that are currently ongoing.

Threshold reported $58.6m cash, equivalents and marketable securities at end December 2014 and has no debt. This has been boosted with the $30m gross/$28.2m net fundraise (8.3m shares at $3.62). Based on our forecasts, which do not include any future milestone income and assume

similar levels of operating spend in coming years, we estimate this level of cash should be sufficient to fund operations into 2017. Threshold could be entitled to development milestones from Merck KGaA before then, which could extend this cash runway.

Threshold has warrants outstanding relating to capital increases in 2011 and 2015. Together, these could bring in around $100m (4m shares with an exercise price of $2.46 expiring in March 2016 from the 2011 capital increase and 8.3m shares with an exercise price of $10.86 with can be exercised from August and expire in 2020).

Exhibit 9: Financial summary

$'000s	2009	2010	2011	2012	2013	2014	2015e	2016e
December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS								
Revenue	0	0	62	5,867	12,495	14,722	14,722	14,722
Cost of Sales	0	0	0	0	0	0	0	0
Gross Profit	0	0	62	5,867	12,495	14,722	14,722	14,722
Research and development	(15,844)	(18,937)	(24,388)	(18,786)	(29,334)	(35,832)	(36,806)	(35,240)
EBITDA	(21,921)	(24,417)	(30,561)	(21,007)	(27,530)	(32,757)	(33,316)	(31,520)
Operating Profit (before amort. and except.)	(21,324)	(23,908)	(30,036)	(19,999)	(26,024)	(31,251)	(32,491)	(31,237)
Intangible Amortisation	0	0	0	0	0	0	0	0
Exceptionals	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0
Operating Profit	(21,324)	(23,908)	(30,036)	(19,999)	(26,024)	(31,251)	(32,491)	(31,237)
Net Interest	(2,324)	5,226	4,383	(51,136)*	(2,189)	9,465	403	477
Profit Before Tax (norm)	(23,648)	(18,682)	(25,653)	(71,135)	(28,213)	(21,786)	(32,088)	(30,760)
Profit Before Tax (FRS 3)	(23,648)	(18,682)	(25,653)	(71,135)	(28,213)	(21,786)	(32,088)	(30,760)
Tax	0	0	0	0	(202)	202	0	0
Profit After Tax (norm)	(23,648)	(18,682)	(25,653)	(71,135)	(28,415)	(21,584)	(32,088)	(30,760)
Profit After Tax (FRS 3)	(23,648)	(18,682)	(25,653)	(71,135)	(28,415)	(21,584)	(32,088)	(30,760)
Average Number of Shares Outstanding (m)	19.6	33.7	45.9	54.2	57.8	60.3	68.7	76.3
EPS - normalised ($)	(1.21)	(0.56)	(0.56)	(1.31)	(0.49)	(0.36)	(0.47)	(0.40)
EPS - normalised and fully diluted ($)	(1.21)	(0.56)	(0.56)	(1.31)	(0.49)	(0.36)	(0.47)	(0.40)
EPS - (IFRS) ($)	(1.21)	(0.56)	(0.56)	(1.31)	(0.49)	(0.36)	(0.47)	(0.40)
Dividend per share ($)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Gross Margin (%)	N/A	N/A	100.0	100.0	100.0	100.0	100.0	100.0
EBITDA Margin (%)	N/A	N/A	-49291.9	-358.1	-220.3	-222.5	-226.3	-214.1
Operating Margin (before GW and except.) (%)	N/A	N/A	-48445.2	-340.9	-208.3	-212.3	-220.7	-212.2
BALANCE SHEET								
Fixed Assets	1,028	561	1,892	1,871	1,745	1,716	1,159	1,159
Intangible Assets	0	0	0	0	0	0	0	0
Tangible Assets	505	271	543	812	686	557	0	0
Investments	523	290	1,349	1,059	1,059	1,159	1,159	1,159
Current Assets	47,657	15,643	20,544	87,650	102,373	66,680	54,066	13,754
Stocks	0	0	0	0	0	0	0	0
Debtors	10,342	944	254	16,802	20,340	8,080	8,067	8,067
Cash	37,315	14,699	20,290	70,848	82,033	58,600	45,999	5,687
Other	0	0	0	0	0	0	0	0
Current Liabilities	(12,874)	(3,514)	(8,591)	(17,451)	(27,016)	(25,974)	(26,210)	(26,177)
Creditors	(12,874)	(3,514)	(8,591)	(17,451)	(27,016)	(25,974)	(26,210)	(26,177)
Short term borrowings	0	0	0	0	0	0	0	0
Long Term Liabilities	(13,154)	(7,747)	(9,362)	(85,923)	(100,577)	(66,398)	(51,678)	(36,958)
Long term borrowings	0	0	0	0	0	0	0	0
Other long term liabilities	(13,154)	(7,747)	(9,362)	(85,923)	(100,577)	(66,398)	(51,678)	(36,958)
Net Assets	22,657	4,943	4,483	(13,853)	(23,475)	(23,976)	(22,663)	(48,222)
CASH FLOW								
Operating Cash Flow	(17,785)	(22,384)	(23,851)	29,913	10,151	(28,288)	(40,987)	(40,507)
Net Interest	45	(130)	(254)	(783)	(1,200)	0	403	477
Tax	0	0	0	0	0	0	51	0
Capex	(22)	(108)	(528)	(482)	(158)	(253)	(268)	(282)
Acquisitions/disposals	0	0	0	0	0	0	0	0
Financing	33,077	6	30,224	21,910	2,392	5,108	28,200	0
Dividends	0	0	0	0	0	0	0	0
Net Cash Flow	15,315	(22,616)	5,591	50,558	11,185	(23,433)	(12,601)	(40,312)
Opening net debt/(cash)	(22,000)	(37,315)	(14,699)	(20,290)	(70,848)	(82,033)	(58,600)	(45,999)
HP finance leases initiated	0	0	0	0	0	0	0	0
Other	0	0	0	0	(0)	(0)	(0)	0
Closing net debt/(cash)	(37,315)	(14,699)	(20,290)	(70,848)	(82,033)	(58,600)	(45,999)	(5,687)

Source: Threshold accounts; Edison Investment Research. Note: *Includes $51m of non-cash charges owing to the change in the fair value of warrants.

Contact details	Revenue by geography
Threshold Pharmaceuticals 170 Harbor Way, Suite 300 South San Francisco, CA 94080 United States +1 650 474 8200 www.thresholdpharm.com	N/A

CAGR metrics		Profitability metrics		Balance sheet metrics		Sensitivities evaluation	
EPS 2011-15e	N/A	ROCE 2014e	N/A	Gearing 2014e	N/A	Litigation/regulatory	●
EPS 2013-15e	N/A	Avg ROCE 2011-15e	N/A	Interest cover 2014e	N/A	Pensions	○
EBITDA 2011-15e	N/A	ROE 2014e	N/A	CA/CL 2014e	N/A	Currency	◖
EBITDA 2013-15e	N/A	Gross margin 2014e	N/A	Stock days 2014e	N/A	Stock overhang	●
Sales 2011-15e	N/A	Operating margin 2014e	N/A	Debtor days 2014e	N/A	Interest rates	○
Sales 2013-15e	N/A	Gr mgn / Op mgn 2014e	N/A	Creditor days 2014e	N/A	Oil/commodity prices	○

Management team

CEO: Harold E "Barry" Selick, PhD

Dr Selick has been at Threshold for more than a decade, having joined as CEO in 2002. He has held senior positions at various biotechnology companies including Affymax (part of GSK), Protein Design Labs and Camitro Corporation. Dr Selick also spent a number of years as a partner at Sofinnova, a VC firm. Dr Selick has a PhD and BS from the University of Pennsylvania.

CMO: Tillman Pearce, MD

Dr Pearce joined Threshold as chief medical officer in 2012. He was previously CMO at KaloBios and has held senior positions in both the US and Europe, including at Novartis, Sanofi and Protein Design Labs. Dr Pearce received his MD from the Medical College of Georgia and is board-certified in both internal medicine and haematology.

SVP Regulatory Affairs and QA: Robert L Simon

Mr Simon joined Threshold in 2012 as SVP of regulatory affairs and quality assurance. He was previously at OSI Pharmaceuticals involved in the approval of Tarceva. Mr Simon has over 30 years of experience of drug development, including at Gilead and BMS. He has a BS in chemistry.

SVP Discovery Research: Mark D Matteucci, PhD

Dr Matteucci joined Threshold in 2002. He has significant experience at a number of healthcare companies, including Gilead, where he established the research programme in nucleic acid targeting, and at Genentech. He has a BS from MIT and a PhD from the University of Colorado.

SVP Clinical Operations and Biostatistics: Stewart M Kroll

Mr Kroll joined Threshold in 2005 and was appointed SVP of Clinical Operations and Biostatistics in 2011. He has experience at both Corixa Corporation and at Coulter Pharmaceuticals. Mr Kroll has a BA and MA in maths from UC Berkeley.

Principal shareholders	(%)
Sutter Hill Ventures	7.51
Federated Investors	7.00
UBS AG	6.21
Blackrock	5.81
JPMorgan Chase & Co	4.20
Baker Bros Advisors LLC	3.44
FMR LLC	3.16
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