EDISON

Threshold Pharmaceuticals

Pipeline update

Tarloxotinib advances into two Phase II trials

Pharma & biotech

Tarloxitinib (TH-4000), Threshold's earlier-stage hypoxia asset, has now started two Phase II studies, as planned. With active development now ongoing we include an indicative valuation for this asset in our rNPV, which has increased to $1,023m ($14.3/share). Tarloxotinib broadens and diversifies Threshold's pipeline beyond evofosfamide, where we continue to expect the number of events needed for analysis of the Phase III STS and pancreatic trials should be reached in H215, with data shortly after.

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	(38.9)	(0.57)	0.0	N/A	N/A
12/16e	14.7	(38.9)	(0.51)	0.0	N/A	N/A

Note: *PBT and EPS are normalised, excluding intangible amortisation, exceptional items.

Start of Phase II trials with tarloxotinib

Threshold has now started two Phase II trials with tarloxotinib: (1) in advanced lung cancer; and (2) in advanced head and neck and skin cancers. We believe both trials could report initial data during 2016, providing key initial insights. Tarloxotinib is a hypoxia activated EGFR-TKI, which could lead to less systemic toxicity, potentially allowing tarloxotinib to overcome dose-limiting rash and diarrhoea associated with current EGFR-TKIs. This mechanism could enable more effective tarloxotinib doses to be administered. Tarloxotinib could also have utility in some cancer patients with poor prognosis where current TKI therapy has limited benefit.

Phase II indications could be significant markets

Currently available EGFR-TKIs for lung cancer generate blockbuster sales. However, a number of patients develop resistance with few treatment options. Erbitux, an EGFR inhibitor, is a leading targeted agent in head and neck cancer and sold nearly $2bn last year. These highlight that significant opportunities could exist in both indications for products that can overcome current limitations.

Key evofosfamide events in H215

With tarloxotinib's planned Phase II trials now underway, the next key events for Threshold will likely relate to evofosfamide. Event-driven Phase III trials are ongoing in both STS (soft tissue sarcoma) and pancreatic cancer. Threshold continues to expect that the number of events required to trigger analysis in each trial could be reached in H215, with top-line data potentially available around YE15.

Valuation: rNPV increases with tarloxotinib inclusion

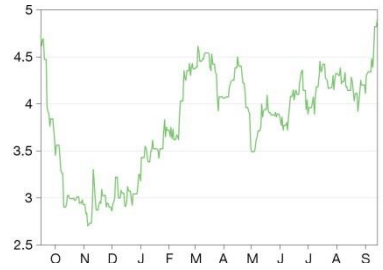
Our Threshold valuation is increased to $1,023m or $14.3/share, including an indicative valuation for tarloxotinib in the two indications now under active Phase II development. Cash at end-June of $67m should be sufficient to fund operations into H216 in the absence of any future milestone income. Threshold is entitled to further evofosfamide development-related milestones, which could become due before H216, and could therefore extend this cash runway.

15 September 2015

Price	**US$4.91**
Market cap	**US$350m**

Net cash ($m) at end June 2015	67.0
Shares in issue	71.3m
Free float	84%
Code	THLD
Primary exchange	NASDAQ
Secondary exchange	N/A

Share price performance



%	1m	3m	12m
Abs	16.9	20.3	0.0
Rel (local)	25.2	29.0	1.7

52-week high/low	US$4.9	US$2.7

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

STS events to trigger Phase III analysis	H215
Pancreatic cancer events to trigger Phase III analysis	H215
Top-line Phase III STS data	Around YE15
Top-line Phase III pancreatic cancer data	Around YE15

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Tarloxotinib advances into two Phase II trials

Tarloxotinib (TH-4000) is a prodrug that, similar to Threshold's lead product evofosfamide, is activated under hypoxic (low oxygen) conditions. Hypoxia-mediated activation of tarloxotinib leads to the release of an irreversible epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI). As a reminder, hypoxia is commonly associated with solid tumours and can lead to resistance to both traditional chemotherapy and radiotherapy, often leading to disease progression. Given this hypoxia activation, tarloxotinib should be relatively inert until release is triggered more selectively in the tumour under hypoxic conditions (rather than in healthy, non-hypoxic tissue). This could lead to lower systemic toxicity and allow for more efficacious doses to be administered to patients without the limitations currently experienced with existing EGFR-TKIs (dose-limiting rash and diarrhoea, for example). Hence, tarloxotinib could potentially lead to improved outcomes for patients.

In addition to this elegant mechanism of activation that exploits conditions particular to hard-to-treat tumours, preclinical data also suggest that tarloxotinib could have activity in certain subsets of patients with poor prognosis where current TKI therapy has limited benefit (as previously described in our last note). Tumours that contain the genetic code (allele) for both mutant and wild type (WT) EGFR (referred to as heterozygous at EGFR) are associated with poorer outcomes. Hypoxia is associated with upregulation of WT-EGFR, and in heterozygous tumours this could be a cause of resistance to current EGFR-TKIs; hence, this is a logical area of development for tarloxotinib.

Threshold has now started two Phase II clinical studies of tarloxotinib to investigate its potential in both advanced lung cancer and in advanced head and neck (H&N) and skin cancers, described in more detail below. Both trials will also measure hypoxia using Threshold's hypoxia imaging agent HX4, which could potentially be used in the future to select responders.

Lung cancer (NSCLC) first off the mark

In August 2015, Threshold announced the start of an open-label Phase II lung cancer trial in a subset of patients with stage IV NSCLC (non-small cell lung cancer). 37 patients with an EGFR mutation who have progressed on a previous EGFR-TKI, and without a T790M mutation (a mutation that leads to resistance to current EGFR-TKIs) will be included in the trial. Patients will receive 150mg/m^2 of tarloxotinib (the maximum tolerated dose, MTD, established in the previous Phase I clinical trial) weekly as part of a four-week cycle. The study is being conducted in collaboration with ATOMIC (Academic Thoracic Oncology Medical Investigators Consortium).

Initial data potentially during 2016

The study will measure overall response rate (ORR) according to RECIST (primary objective) criteria in addition to duration of response, progression-free survival (PFS), overall survival (OS) and safety and tolerability (secondary objectives). According to clinicaltrials.gov, primary endpoint data could become available during H216, although we believe interim data could become available before this providing some early insights into tarloxotinib's potential efficacy.

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% of which around 15% in the US have EGFR mutations. Nearly 60% of lung cancer patients have advanced disease and around half of lung cancer patients develop resistance owing to T790M mutations. Assuming that most first-line patients progress, requiring further treatment, this suggests a potential target patient market for tarloxotinib in NSCLC in the US alone of around 8-9k new patients each year. If we assume that tarloxotinib can achieve similar pricing as we estimate for evofosfamide ($80k per patient per year),

this suggests a total market opportunity based on available patients in the US of around $700m, with likely similar in the major European countries.

Combined sales of current treatments >$1bn

Current EGFR-TKIs approved for the treatment of lung cancer overexpressing EGFR mutations include erlotinib (Tarceva), afatinib (Gilotrif) and gefitinib (Iressa). Reported US sales for Tarceva were $305m in the 12 months ending March 2015 (although approval is not limited to NSCLC) and $444m in total worldwide sales. Iressa sales were $623m in 2014, although this does not include any contribution from the US as approval in NSCLC was only recently granted. Gilotrif sales are not specifically disclosed, to our knowledge.

With T790M mutations occurring in around 50% of patients who develop resistance to current EGFR-TKIs, it is not surprising that there are already products in development to address these specific patients, including rociletinib (Clovis Oncology) and AZD9291 (AstraZeneca), both of which were recently filed in the US and Europe. However, there are limited options for patients who develop resistance to current EGFR-TKIs owing to other mechanisms. Tarloxotinib addresses other mechanisms of current EGFR-TKI resistance not due to the T790M mutation.

Head and neck cancer (H&N) not far behind

Threshold has more recently announced the start of a Phase II trial with tarloxotinib in second-line advanced head and neck (H&N) and skin cancer. The trial is an open label, single-arm study and will include up to 68 patients with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN) or skin (SCCS); patients who have received prior treatment with an anti-EGFR antibody therapy (cetuximab/Erbitux is approved in SCCHN) can be recruited into the trial (although patients who have received prior EGFR-TKI treatments are excluded from the trial).

Initial data could also become available during 2016

In common with the NSCLC trial, this SCCHN/SCCS study will also measure overall response rate (ORR) according to RECIST (primary objective) criteria in addition to duration of response, progression-free survival (PFS), overall survival (OS) and safety and tolerability (secondary objectives). Initial primary endpoint data are expected in early 2017 (according to clinicaltrials.gov) although we believe some interim data could potentially be released earlier than this.

The National Cancer Institute estimates that there are around 52,000 new cases of H&N cancer per year in the US, of which around 90% are squamous cell. About half of patients present with advanced disease. The incidence of skin cancer is vast, with the American Cancer Society estimating that there are around 3.5 million new non-melanoma skin cancers in the US each year, of which around 20% are squamous cell, ie 700,000 SCCS. However, the disease is generally caught early and the number of deaths from non-melanoma skin cancer, a proxy for the number of patients with advanced disease, is estimated at around 2,000 each year. Taking these two patient populations and assuming that the majority will require second-line treatment, this suggests a potential target SCCHN/SCCS patient market in the US for tarloxotinib of around 19k new patients each year, with likely similar in the major European countries. Based on a price of $80k per patient per year (in-line with our assumption for evofosfamide), this suggests a total market opportunity based on eligible patients in the US of around $1.5bn. Erbitux, which is approved in a number of indications including H&N cancer, generated sales of nearly $2bn in 2014 ($723m in the US in 2014 and €903m or c $1.2bn in the rest of world).

Valuation

We have updated our Threshold rNPV-based valuation to $1,023m (from $949m) or $14.3/share to now include an illustrative contribution for tarloxotinib given it is in active Phase II development. More details are provided below. The breakdown of our rNPV base-case valuation, which includes last reported net cash of $67m and uses a 12.5% discount rate, is shown in Exhibit 1. Aside from the inclusion of tarloxotinib, our valuation has been rolled forwards with time, although no major revisions have been made to our underlying evofosfamide assumptions. These include 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. With Q215 financial results Threshold announced that the Phase II trial of evofosfamide in melanoma is being closed owing to slower than expected recruitment in addition to an evolving treatment landscape; this indication was not specifically included in our valuation, so has no impact on our rNPV.

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.

Exhibit 1: 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	425.9	60	251.4	3.5
	Pancreatic cancer	2017	$3.5bn	40	1,400	980.4	50	483.5	6.8
	NSCLC	2018	$5.0bn	15	740	335.2	40	128.3	1.8
	GBM	2020	$540m	30	160	58.8	30	17.0	0.2
	r/r MM	2020	$1.3bn	20	260	93.4	30	26.2	0.4
Tarloxotinib	NSCLC, SCCHN/SCCS	2021	NSCLC $1.4bn	25	950	431.1	20	50.1	0.7
			SCCHN/SCCS $3.0bn	20					
Net cash						67.0	100	67.0	0.9
Valuation						**2,391.8**		**1,023.4**	**14.3**

Source: Edison Investment Research

For tarloxotinib, and consistent with our evofosfamide valuation, we have estimated the potential market opportunity in the indications where Phase II trials are ongoing and have applied base-case market share assumptions to arrive at peak sales forecasts for the purposes of our valuation. At this stage and in the absence of significant human efficacy data, assessing the market dynamics and likely uptake of tarloxotinib is challenging, so our valuation aims to provide an indication of tarloxotinib's potential using fairly standard assumptions.

As described earlier in the report, the potential market opportunity in the US and Europe for tarloxotinib could be around $1.4bn in NSCLC and around $3bn in SCCHN/SCCS based on currently available patient numbers and assuming average US pricing of $80k per patient per year (in-line with our current estimate for evofosfamide). Based on our current indicative base-case penetration of 20-25%, tarloxotinib could therefore have almost blockbuster potential in these two indications alone.

Our valuation assumes that Threshold will fully conduct the ongoing Phase II trials. However, potential costs beyond this are somewhat uncertain, as these will depend on a number of factors, including any partnering strategy. At this stage, Threshold has not made any comments on the future of tarloxotinib regarding partnering or commercialisation and we believe this could also

depend on future decisions regarding the co-promote/co-commercialisation evofosfamide options in the US. For the purposes of our valuation, and consistent with evofosfamide, we assume that Threshold will participate in funding a portion of the future Phase III development, in exchange for a share of future profits (equating to a margin on future sales of around 30%). These assumptions will all be subject to future revisions as tarloxotinib development and the future strategy evolves.

We assume launch from 2021, allowing for five years of development post availability of initial Phase II efficacy data next year. Although there is limited human efficacy data available to date for tarloxotinib, we apply a 20% probability of success, which takes into consideration the validated mechanism of action (EGFR-TKI).

Financials

Threshold reported Q215 revenue of $3.7m consisting entirely of deferred revenue from the $110m of milestones already received under the deal with Merck KGaA. R&D spend was $10.1m and SG&A was $2.5m. We have made no changes to our FY15 revenue or SG&A forecasts, as these are broadly in-line with the quarterly trends. However, with the start of two Phase II trials, we have increased our FY15 R&D forecast to $42.4m (from $36.8m) as we do assume there will be an uptick in R&D spend in H215 (H115 R&D costs were $20.8m). This leads to a corresponding net loss increase. We continue to assume that R&D spend in future years will remain at similar levels to 2015, although this will depend on future development of both evofosfamide and tarloxotinib.

Threshold reported $67.0m cash, equivalents and marketable securities at end Q215 and has no debt. With our higher R&D spend leading to increased cash burn, we now assume this will be sufficient to fund operations to H216 (we previously estimated cash would last into 2017). However, our forecasts do not include any future milestone income (Threshold could be entitled to a further $100m of evofosfamide development-related milestones, which we assume are linked to filing and approval), which could become due before H216 and could therefore extend this cash runway. For illustrative purposes only, and in the absence of unknown/uncertain future milestone payments, our 2016 forecasts include financing of $5.7m to allow Threshold to fund operations to the end of 2016, which we include as long-term debt.

Exhibit 2: Financial summary

$000s	2009	2010	2011	2012	2013	2014	2015e	2016e
Year-end 31 December	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP	US GAAP
PROFIT & LOSS								
Revenue	0	0	62	5,867	12,495	14,722	14,722	14,722
Cost of Sales	0	0	0	0	0	0	0	0
Gross Profit	0	0	62	5,867	12,495	14,722	14,722	14,722
Research and development	(15,844)	(18,937)	(24,388)	(18,786)	(29,334)	(35,832)	(42,400)	(42,940)
EBITDA	(21,921)	(24,417)	(30,561)	(21,007)	(27,530)	(32,560)	(38,863)	(39,173)
Operating Profit (before amort. and except.)	(21,324)	(23,908)	(30,036)	(19,999)	(26,024)	(31,251)	(38,085)	(38,937)
Intangible Amortisation	0	0	0	0	0	0	0	0
Exceptionals	0	0	0	0	0	0	0	0
Other	0	0	0	0	0	0	0	0
Operating Profit	(21,324)	(23,908)	(30,036)	(19,999)	(26,024)	(31,251)	(38,085)	(38,937)
Net Interest*	(2,324)	5,226	4,383	(51,136)	(2,189)	9,465	(862)	0
Profit Before Tax (norm)	(23,648)	(18,682)	(25,653)	(71,135)	(28,213)	(21,786)	(38,947)	(38,937)
Profit Before Tax (reported)	(23,648)	(18,682)	(25,653)	(71,135)	(28,213)	(21,786)	(38,947)	(38,937)
Tax	0	0	0	0	(202)	202	0	0
Profit After Tax (norm)	(23,648)	(18,682)	(25,653)	(71,135)	(28,415)	(21,584)	(38,947)	(38,937)
Profit After Tax (reported)	(23,648)	(18,682)	(25,653)	(71,135)	(28,415)	(21,584)	(38,947)	(38,937)
Average Number of Shares Outstanding (m)	19.6	33.7	45.9	54.2	57.8	60.3	68.8	76.4
EPS - normalised ($)	(1.21)	(0.56)	(0.56)	(1.31)	(0.49)	(0.36)	(0.57)	(0.51)
EPS - normalised and fully diluted ($)	(1.21)	(0.56)	(0.56)	(1.31)	(0.49)	(0.36)	(0.57)	(0.51)
EPS - (reported) ($)	(1.21)	(0.56)	(0.56)	(1.31)	(0.49)	(0.36)	(0.57)	(0.51)
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	-221.2	-264.0	-266.1
Operating Margin (before GW and except.) (%)	N/A	N/A	-48445.2	-340.9	-208.3	-212.3	-258.7	-264.5
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	49,844	8,567
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	41,778	500
Other	0	0	0	0	0	0	0	0
Current Liabilities	(12,874)	(3,514)	(8,591)	(17,451)	(27,016)	(25,974)	(26,473)	(26,538)
Creditors	(12,874)	(3,514)	(8,591)	(17,451)	(27,016)	(25,974)	(26,473)	(26,538)
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)	(52,654)	(43,649)
Long term borrowings	0	0	0	0	0	0	0	(5,715)
Other long term liabilities	(13,154)	(7,747)	(9,362)	(85,923)	(100,577)	(66,398)	(52,654)	(37,934)
Net Assets	22,657	4,943	4,483	(13,853)	(23,475)	(23,976)	(28,123)	(60,460)
CASH FLOW								
Operating Cash Flow	(17,785)	(22,384)	(23,851)	29,913	10,151	(27,735)	(44,966)	(46,757)
Net Interest	45	(130)	(254)	(783)	(1,200)	(994)	114	0
Tax	0	0	0	0	0	0	51	0
Capex	(22)	(108)	(528)	(482)	(158)	(224)	(221)	(236)
Acquisitions/disposals	0	0	0	0	0	0	0	0
Financing	33,077	6	30,224	21,910	2,392	5,520	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)	(16,822)	(46,992)
Opening net debt/(cash)	(22,000)	(37,315)	(14,699)	(20,290)	(70,848)	(82,033)	(58,600)	(41,778)
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)	(41,778)	5,215

Source: Threshold accounts; Edison Investment Research. Note: *Includes non-cash charges owing to the change in the fair value of warrants ($9.3m income in 2014; $2.3m expense in 2013 and $51m expense in 2012).

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