Trinity Delta

HUTCHMED

Update

Data at EHA 2024 heighten focus on sovleplenib

25 June 2024

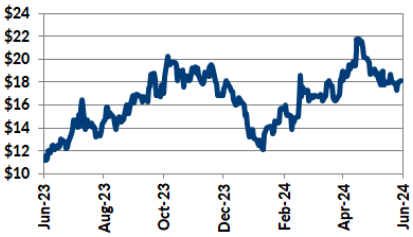
HUTCHMED's clinical data presentations at the European Hematology Association (EHA) 2024 congress have provided meaningful insights into sovleplenib's efficacy and safety profile. This is the first HUTCHMED immunology/haem-oncology asset to be filed in China, with a potential approval decision in ≥2L immune thrombocytopenia (ITP) expected late-2024. The prospect of China approvals for sovleplenib and follow-on indications for fruquintinib, as well as the first potential fruquintinib regulatory decision for advanced metastatic colorectal cancer (mCRC) in Japan (following its recent European approval) could round off a busy 2024. Continued commercial execution underpins the FY24 expectation for Oncology/Immunology consolidated revenues of $300-$400m, driven by targeted 30-50% growth in marketed product sales and royalties. Our HUTCHMED valuation is increased c 5% to $6.10bn/£5.09bn/HK$47.61bn, or $35.03/ADS and 584p/HK$54.64 per share.

Year-end: December 31	2022	2023	2024E	2025E
Revenues ($m)	426.4	838.0	611.7	771.3
Adj. PBT ($m)	(410.4)	58.3	(167.9)	(40.6)
Net Income ($m)	(360.8)	100.8	(120.8)	8.8
Earnings per ADS ($)	(2.13)	0.59	(0.71)	0.05
Cash ($m)	631.0	886.3	757.8	746.4
Adj. EBITDA ($m)	(349.3)	73.9	(129.5)	7.2

Source: Trinity Delta Note: Adjusted PBT excludes exceptionals, Cash includes short-term investments, Adjusted EBITDA includes equity in earnings of equity investees, $ refers to USD unless otherwise specified

- **Positive sovleplenib data at EHA** Results of the ESLIM-01 Phase III study in ITP confirmed a durable response rate of 48.4% and overall response rate of 70.6% at week 24, in a heavily pre-treated patient population. Efficacy and tolerability data suggest a competitive profile vs other approved/late-stage small molecule drugs, including first-in-class Syk inhibitor fostamatinib. Phase II proof of concept data were also presented in a second immunology indication, as well as initial Phase I results in Hodgkin's Lymphoma.
- **Next steps for sovleplenib** The China NDA in ≥2L ITP was accepted for Priority Review in January 2024, with an approval decision expected around end-2024. Launch planning is underway, with a modest specialty immunology sales and marketing team expected to be in place by year-end, supplementing HUTCHMED's existing commercial infrastructure. For ex-China global markets, an international Phase Ib bridging study has started enrolment, and regulatory discussions are ongoing regarding the design of the Phase III programme. A strategic partner is sought for further global development and commercialisation.
- **Update valuation of $35.03/ADS or 584p/HK$54.64 per share** Based on the detailed sovleplenib ITP data we increase our China peak sales in this indication to $300m (from $200m) and now also include a token $50m peak sales in a second indication (rare disease wAIHA). With sovleplenib filed for approval in China, we increase our success probability to 95% (from 85%). These changes to our sovleplenib assumptions in China result in an overall +5% uplift to our HUTCHMED valuation, with this increased to $6.10bn/£5.09bn/HK$47.61bn or $35.03/ADS and 584p/HK$54.64 per share.

Price (US ADS)	$18.14
(UK share)	288p
(HK share)	HK$28.55
Market Cap	$3.16bn £2.51bn HK$24.87bn
Enterprise Value	$2.27bn £1.81bn HK$17.95bn
Shares in issue (ADS)	174.3m
(shares)	871.3m
12 month range	$10.97-$21.92 173.6p-353.0p HK$17.44-35.90
Free float	61.8%
Exchanges	NASDAQ AIM SEHK
Sector	Healthcare
Company codes	HCM HCM.L 0013.HK
Corporate client	Yes



Company description

HUTCHMED is a Hong Kong headquartered biopharma focused on discovering, developing and commercialising innovative targeted therapeutics and immunotherapies to treat cancer and autoimmune diseases. It has a diverse pipeline of first-in-class/best-in-class selective oral TKIs in development for the China and global markets.

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HUTCHMED: spotlight on sovleplenib

HUTCHMED is steadily executing on its strategy to achieve sustainable profitability from FY25, centred around commercial delivery and near-term value creation from the most advanced in-house pipeline assets as the company transitions into a fully integrated commercial enterprise addressing the significant global market opportunity with its Oncology/Immunology products. Commercial traction in China is building for first wave products, partner Takeda has launched the first HUTCHMED product in the US and European approval has just been granted, and key pipeline programmes are progressing with multiple near-term clinical and regulatory catalysts for new indications, new markets, and new products. Sovleplenib, currently under review in China for ≥2L ITP (immune thrombocytopenia), is one such asset. In our view, HUTCHMED is a unique biopharma opportunity with a broad pipeline of largely de-risked late-stage assets, global ambitions supported by large pharma partners, proven commercial execution in China yielding a growing top line, all balanced with shrewd investment. Our updated HUTCHMED valuation is $6.10bn/ £5.09bn/ HK$47.61bn, equivalent to $35.03/ADS or 584p/HK$54.64 per share.

EHA presentations paint positive picture of sovleplenib's clinical profile…

Clinical data presentations at the European Hematology Association (EHA) 2024 congress have provided meaningful insights into the profile of sovleplenib, the first of HUTCHMED's immunology/haem-oncology assets to be filed with the China regulator. Sovleplenib is currently under review in China for ≥2L immune thrombocytopenia (ITP), a chronic disease with high unmet need. Data from the ESLIM-01 Phase III study confirmed a durable response rate of 48.4% and overall response rate of 70.6% at week 24, in a heavily pre-treated patient population.

…suggesting sovleplenib will help underpin near- and medium-term sales growth

Sovleplenib is one of several late-stage programmes, which alongside currently marketed drugs, will contribute to HUTCHMED's goal of achieving sustainable profitability from FY25. Continued commercial delivery should help achieve guided FY24 Oncology/Immunology consolidated revenues of between $300m and $400m, driven by targeted 30-50% growth in marketed product sales and royalties. Our April 2024 Outlook provides a detailed breakdown of our forecasts.

China approval likely late-2024, with deal for ex-China expected in a similar time frame

A sovleplenib China approval decision is anticipated in late-2024. For global, ex-China markets, HUTCHMED is seeking a partner for further development and commercialisation beyond the recently initiated international Phase Ib bridging study. EHA 2024 presentations of China Phase III data in ITP, which suggest that sovleplenib has a more attractive efficacy and safety profile to the first-in-class Syk inhibitor Rigel's fostamatinib (approved as Tavalisse in the US, Europe, and Japan), plus confirmation of proof of concept in a second rare immunology indication, wAIHA, could catalyse such a deal in our view.

Multiple additional pipeline catalysts anticipated in 2024

Beyond sovleplenib, several important events are expected during 2024, including potential Japan approval for fruquintinib (advanced mCRC) following the grant of European approval by the EMA in June, and China approval decisions for fruquintinib (2L gastric cancer, and 2L endometrial cancer PD-1 checkpoint inhibitor combination). Regulatory filings, subject to positive data, are also planned for tazemetostat (China: 3L follicular lymphoma), and potentially savolitinib (global: 2/3L NSCLC) if SAVANNAH data support accelerated approval.

Sovleplenib: HUTCHMED's first immunology asset

Sovleplenib is gaining investors' attention as clinical data highlight commercial potential

Investors are increasingly focused on the prospects for sovleplenib, a wholly-owned best-in-class oral small-molecule Syk (spleen tyrosine kinase) inhibitor, which is the most advanced of HUTCHMED's next wave of haem-oncology/ immunology assets. Sovleplenib has Breakthrough Therapy designation in China, and the China NDA for the treatment of 2L immune thrombocytopenia (ITP) was accepted for Priority Review in January 2024, with an approval decision expected around end-2024.

Existing China infrastructure set to be bolstered by a c 100 specialty sales team

HUTCHMED already has much of the necessary infrastructure in place to support sovleplenib commercialisation in China, although this will be supplemented by a c 100-strong specialty immunology sales and marketing team. We expect this to be in place by year-end, ready for the first meaningful sovleplenib sales contribution from 2025, subject to approval in ITP.

Sovleplenib is HUTCHMED's first immunology product, initially targeting ITP and wAIHA

If approved by the China regulator, sovleplenib would become HUTCHMED's first immunology product. While Syk is a validated target in rheumatoid arthritis, HUTCHMED has initially pursued orphan immune disorders which require smaller clinical programmes; however, further development could include selected haematological cancers, specifically B-cell malignancies. Clinical data presentations at the European Hematology Association (EHA) 2024 congress include results from sovleplenib studies in the lead indication of ITP (detailed Phase III results), the second immunology indication of warm antibody autoimmune hemolytic anemia (wAIHA, Phase II proof of concept), as well as the haematological malignancy, Hodgkin's Lymphoma (Phase I first in human).

Ex-China regulatory pathways are being clarified; Phase III will likely be decided by a partner

HUTCHMED's strategy of focused in-house R&D investment and partnering of its assets for later-stage international development mean that business development activities around sovleplenib will intensify. The company has had meetings with the FDA to discuss clinical plans and clarify the regulatory pathway, and recently began enrolling into an international Phase Ib bridging study. However, we expect that HUTCHMED will partner sovleplenib ahead of initiating ex-China Phase III registrational studies. EHA 2024 presentations of China Phase III data in ITP plus confirmation of proof of concept in wAIHA could be the catalyst for such a deal.

ITP: an autoimmune disorder with significant unmet need

ITP is a complex disease with sub-optimal treatment regimens currently

ITP (immune thrombocytopenia) is an acquired chronic autoimmune disorder characterised by low platelet counts (<100×10^9/L) leading to increased bleeding risk, bruising, fatigue, and decreased quality of life. The reduction in platelet count is caused by IgG autoantibodies targeting glycoproteins expressed on platelets and megakaryocytes (hematopoietic bone marrow stem cells that are precursors to platelets) resulting in the self-destruction of platelets via increased clearance, inhibition of production, and impairment of their function.

Existing therapies have limited efficacy and high side-effects

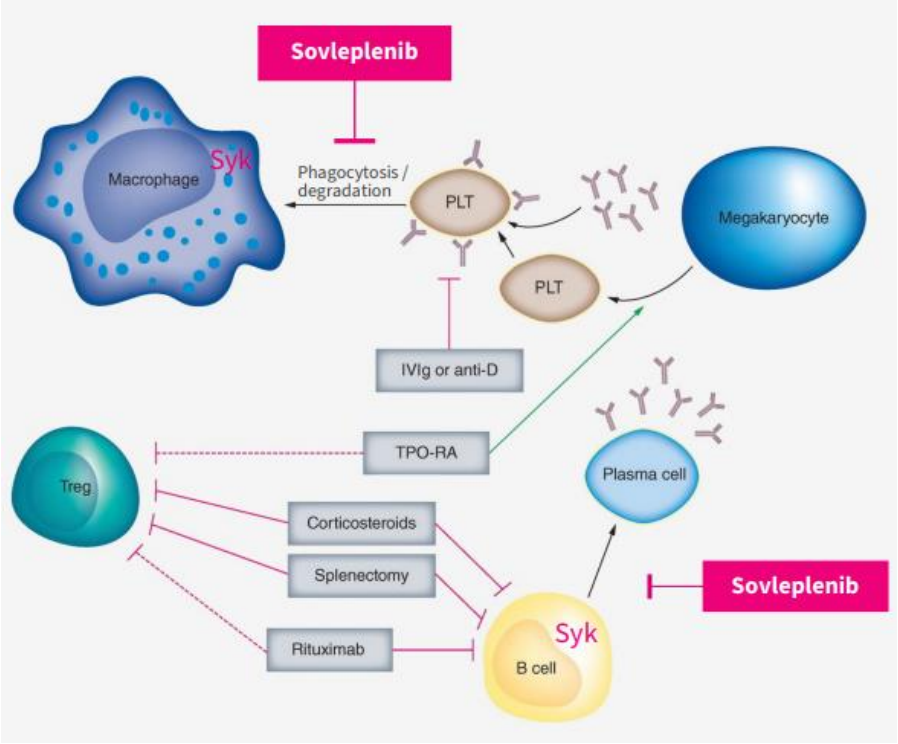
There is a need for improved ITP therapies as current treatment options are associated with comorbidities, have limited efficacy and duration of effect, and have only a modest impact on quality-of-life measures. Currently, the main strategies for treating ITP involve: (1) suppressing the aberrant immune response (with corticosteroids or anti-CD20 antibody rituximab); (2) stimulating platelet

production (using thrombopoietin/thrombopoietin receptor agonists [TPO/TPO-RA]); and (3) suppressing platelet clearance (via splenectomy).

Different geographies have different standards of care

In China, standard of care typically includes first-line (1L) use of corticosteroids, followed by TPO/TPO-RA in the 2L setting. However, ultimately, most patients become refractory to treatment, and so run out of options, or are lost to follow up for other reasons. A broader range of therapies are approved in the US and Europe, with 1L treatments including corticosteroids, intravenous immunoglobulin (IVIG), and anti-RhD immune globulin. Again, the lack of durable remission, or intolerance to steroids, means c 68% of adult patients require subsequent treatment such as TPO-RAs (ie romiplostim, eltrombopag, or avatrombopag) or rituximab (off-label), other immunosuppressive agents (such as azathioprine, cyclophosphamide, cyclosporine, or mycophenolate), or, in chronic cases, surgery (splenectomy as the spleen not only produces antibodies but is a site of platelet destruction). Hence, significant unmet needs remain.

Exhibit 1: Mechanism of action of sovleplenib and other therapies in ITP



Source: HUTCHMED Note: anti-D = anti-D immunoglobulin; IVIG = IV immunoglobulin; PLT = platelet; TPO-RA = thrombopoietin receptor agonists

Rigel's fostamatinib is the first-in-class Syk inhibitor, approved in the US, EU, and Japan

One of the more recently approved therapies for 2L ITP is Tavalisse (fostamatinib, Rigel); to date it is the only approved small molecule drug specifically targeting Syk in the US (2018), EU (2019), and Japan (2022). It is a twice daily drug with modest efficacy – an 18% durable response rate (DRR) and 43% overall response rate (ORR) – and dose limiting toxicities (including diarrhoea, hypertension, nausea, and liver toxicity). Syk plays a central role in B-cell activation and proliferation, and fostamatinib has validated Syk as a target in ITP. Syk inhibition presents a different mechanism of action to other ITP therapies (Exhibit 1). Rather than boosting platelet production, Syk inhibition prevents the immunological destructions of platelets through targeting of both B-cells (to inhibit antiplatelet autoantibody production) and macrophages (impeding their phagocytosis of autoantibody-bound platelets).

Detailed ESLIM-01 data at EHA

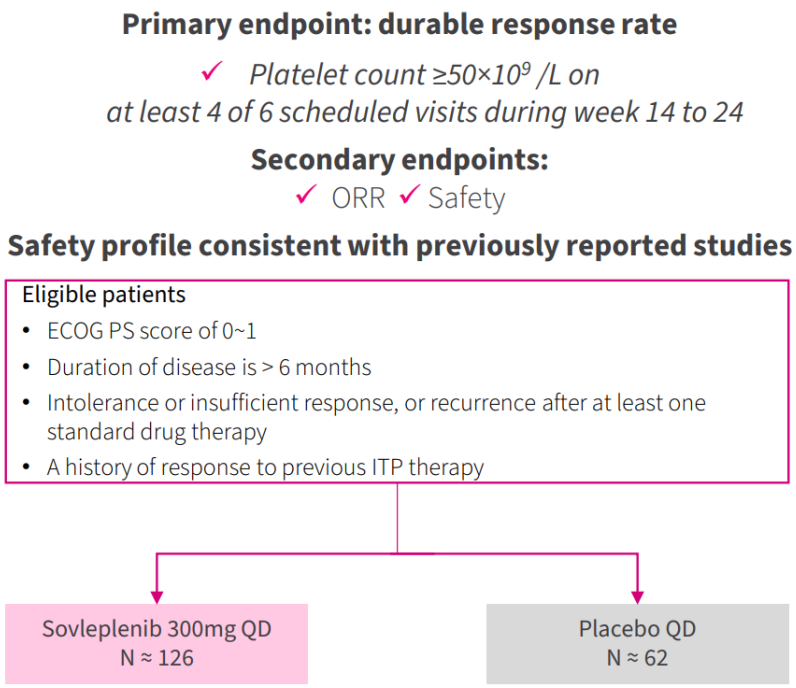
Sovleplenib appears to be highly effective and well differentiated

Sovleplenib is differentiated from fostamatinib with greater selectivity for Syk, a once-daily dosing schedule (vs twice daily), and a more favourable DRR of 40% in Phase II and 48.4% in Phase III (vs 18% for fostamatinib). Detailed results of the randomised, double-blind, placebo-controlled ESLIM-01 Phase III monotherapy study in 2L ITP, reported at EHA 2024 and also published in The Lancet Haematology (June 2024), have provided further supporting evidence that sovleplenib has a more attractive efficacy and safety profile than fostamatinib, including in heavily pre-treated patients.

Encouraging efficacy and a cleaner side-effect profile

Sovleplenib's China NDA was supported by positive data from the ESLIM-01 study (Exhibit 2) in previously treated adult patients with primary ITP. This trial met its primary endpoint of a clinically meaningful and statistically significant increase in durable response rate (DRR) in sovleplenib treated relapsed/refractory ITP patients in China vs those on placebo (48.4% vs zero, p<0.0001), as well as all secondary endpoints including safety. The latter is particularly important given that ITP is a chronic condition, and first- and second-generation Syk inhibitors are associated with severe off-target toxicities (diarrhoea, hypertension, liver toxicity) that limit their use.

Exhibit 2: ESLIM-01 trial design



Source: HUTCHMED

Full ESLIM-01 data show early and durable clinical responses

Detailed ESLIM-01 data presented at EHA 2024 confirmed that patients treated with sovleplenib demonstrated a clinically meaningful early and sustained durable platelet response, with a DRR of 48.4% (vs zero for placebo, p<0.0001) and a median time to response of 1.1 weeks (vs 4.3 weeks). Median treatment duration was 24.1 weeks for sovleplenib vs 12.1 weeks for placebo, with 68.3% of those in the sovleplenib arm receiving treatment for 24 weeks (vs 12.9% for placebo).

Material improvements in secondary endpoints and in quality of life measures

Key secondary endpoints were ORR and safety. ORR (defined as at least one platelet count over the ≥50x10^9/L threshold, not caused by rescue therapy) was significantly higher for sovleplenib at 68.3% vs 14.5% for placebo in weeks 0-12, and 70.6% vs 16.1% respectively in weeks 12-24 (both p<0.0001). Sovleplenib's safety profile was tolerable, with a similar level of Grade 3 or above treatment-emergent adverse events (TEAEs) as placebo (25.4% vs 24.2%). The most frequent TEAEs with sovleplenib were upper respiratory tract infections (28.6% vs 9.7%), COVID-19 infection (23.8% vs 12.9%), and increased blood lactate dehydrogenase (23.8% vs 6.5%); most incidences were mild/moderate and resolved either spontaneously or with intervention. Sovleplenib also significantly improved quality of life in physical functioning and energy/fatigue (p<0.05).

For context, the sovleplenib Phase Ib/II study (The Lancet Haematology) in relapsed/refractory primary ITP reported an ORR of 80% and DRR of 40% in a heavily pre-treated patient group, with a median treatment duration of 142 days (range: 23-170), and similar levels of efficacy in patients with or without prior treatment with TPO/TPO-RA (ie eltrombopag or romiplostim).

Prespecified sub-group analyses show consistent benefit in heavily pre-treated patients

Most patients enrolled in the ESLIM-01 study had ITP for three years or longer (77.7%) and were heavily pre-treated, with a median of four prior lines of therapy; the majority (71.3%) had received prior TPO/TPO-RA treatment. A post-hoc subgroup analysis evaluating the impact of prior lines of anti-ITP therapy on the efficacy and safety of sovleplenib treatment showed a consistent clinical benefit for both DRR and ORR in patients receiving ≤3, 4, and ≥5 lines of prior therapy (Exhibit 3), with a lower percentage of sovleplenib-treated patients (in all three prior lines of therapy subgroups) receiving rescue therapy vs placebo. Additionally, while more TEAEs were reported in patients treated with sovleplenib (99.2%) vs 85.5% in the placebo group, these were similar across the different prior-line subgroups, and most were Grade 1-2 (≥Grade 3 TEAEs were 25.4% vs 24.2% in the sovleplenib and placebo arms, respectively). In both the sovleplenib and placebo arms, the ≥5L therapy group had higher SAE incidence than in the patient groups that had received fewer prior lines of therapy.

Exhibit 3: ESLIM-01 efficacy analyses by prior lines of therapy

Outcome	≤3 prior lines		4 prior lines		≥5 prior lines	
	Sovleplenib (n=38)	Placebo (n=20)	Sovleplenib (n=29)	Placebo (n=22)	Sovleplenib (n=59)	Placebo (n=20)
DRR %	50.0	0	55.2	0	41.1	0
p-value	p<0.0001		p<0.0001		p<0.0001	
ORR %	81.6	40.0	62.1	9.1	67.8	0
p-value	p=0.0013		p=0.0009		p<0.0001	
Rescue therapy use %	18.4%	20.0%	17.2%	36.4%	28.8%	50.0%

Source: HUTCHMED; EHA 2024 (poster: P1629) Note: DRR = durable response rate; ORR = overall response rate

Consistent platelet improvement across multiple prior treatment patient groups

The post hoc sub-group analysis assessing the impact of prior TPO/TPO-RA treatment on the efficacy of sovleplenib in ITP patients demonstrated that it consistently improved platelet counts in primary ITP patients previously treated with TPO/TPO-RA, irrespective of the TPO/TPO-RA treatment type or number of prior regimens (Exhibit 4). Overall, in ESLIM-01, 71.3% (134 of 188) of enrolled patients had received prior TPO/TPO-RA treatment; of these DRR was 46.8% for sovleplenib vs zero on placebo, with an ORR of 68.1% (vs 7.5%) respectively.

Exhibit 4: ESLIM-01 efficacy analyses by prior TPO/TPO-RA exposure

Outcome	TPO only		TPO-RA only		TPO and TPO-RA		1 TPO/TPO-RA regimens		≥2 TPO/TPO-RA regimens	
	Sovle (n=29)	Placebo (n=8)	Sovle (n=34)	Placebo (n=19)	Sovle (n=31)	Placebo (n=13)	Sovle (n=51)	Placebo (n=16)	Sovle (n=43)	Placebo (n=24)
DRR %	58.6	0	47.1	0	35.5	0	51.0	0	41.9	0
p-value	p=0.0012		p=0.0003		p=0.0060		p<0.0001		p<0.0001	
ORR %	72.4	25.0	73.5	5.3	58.1	0	70.6	12.5	65.1	4.2
p-value	p=0.0137		p<0.0001		p=0.0004		p<0.0001		p<0.0001	

Source: HUTCHMED; EHA 2024 (poster: P1631) Note: DRR = durable response rate; ORR = overall response rate

Putting ESLIM-01 into context

Despite limitations of cross-trial comparisons, data are supportive of best-in-class profile

The importance of the ESLIM-01 data centres on reinforcing sovleplenib's best in class efficacy, safety, and dosing profile vs fostamatinib and, despite the limitations of cross-trial comparisons, providing an indication of comparative efficacy vs existing and developmental stage drugs for ≥2L ITP. The magnitude of its effect and durability of response in heavily pretreated ITP patients could have a significant impact on sovleplenib's potential market uptake, while its tolerability over the current duration of treatment (24 weeks) is promising and is a critical factor for a chronic medication in an indication where treatment discontinuations due to side-effects and/or lack of efficacy are common. As shown in Exhibit 5, ESLIM-01 efficacy data compare favourably with that from key studies of other novel agents in ≥2L ITP.

Exhibit 5: Comparison of ESLIM-01 efficacy data (over 24 weeks) with other key studies in 2L ITP

Drug candidate (company)	Sovleplenib (HUTCHMED)	Rilzabrutinib (Sanofi)	Efgartigimod* (Argenx)	Fostamatinib** (Rigel)
Clinical study	ESLIM-01 Phase III	LUNA-2 Phase I/II Part B	ADVANCE IV Phase III	FIT-1 and FIT-2 Phase III
Data presented	EHA 2024	ASH 2023	ASH 2022	BJHaem 2020
DRR %	48.4%	35.0%	21.8%	18%
ORR %	70.6% (24 wks)	61.5%	-	43%
Rescue therapy use %	22.2%	12%	-	30%

Source: Trinity Delta; HUTCHMED, company websites Note: DRR = durable response rate; ORR = overall response rate; * = approved for ITP in Japan; ** = approved for ITP in US, Europe, and Japan

Competitor clinical profiles provide opportunities for differentiation

Of the three comparators in Exhibit 5, fostamatinib is the only currently approved oral therapy (as Tavalisse in the US, Europe, and Japan), while efgartigimod is only approved in Japan (as Vyvgart) after delivering mixed results in its Phase III registrational programme. The efgartigimod ADVANCE study met its primary endpoint, but a second trial, ADVANCE-SC, showed no significant difference from placebo on all key outcome measures. Sanofi intends to make US and EU regulatory submissions for its Bruton tyrosine kinase (BTK) inhibitor rilzabrutinib in ITP during 2024, after positive top line results for the Phase III LUNA-3 trial were reported in April 2024; detailed data from this study are expected to be presented at a scientific meeting later in 2024.

We also note that the DRR and ORR for sovleplenib (48.4% and 70.6% respectively) was similar to TPO-RAs (ranging between 38-49% for DRR and 79-83% for ORR), even though 71.3% of patients in the ESLIM-01 study had previously been treated with TPO/TPO-RA.

ITP data could stimulate US partnering interest

Sovleplenib profile should be attractive to potential ex-China partners for global markets

Outside China, following discussions with regulators HUTCHMED has now initiated an international dose finding study for sovleplenib. The two-part open label Phase Ib bridging study aims to enrol 48 adult patients with primary ITP at centres across the US, Europe, and Australia. Part 1 of the trial consists of a standard 3+3 dose escalation design; two selected sovleplenib doses will then be evaluated in a 1:1 randomised dose optimisation stage (Part 2) over an initial 24-week treatment period with a 24-week observational post-treatment follow up. The primary endpoints of this study are safety focused (ie dose-limiting toxicities, and adverse events, including bleeding related events); secondary endpoints include ORR, DRR, time to response (TTR), and treatment free platelet response.

Partner sought for ex-China development

The aim of the study is to determine the recommended sovleplenib Phase III dose (RP3D) for international registrational trials in ≥2L ITP. An ex-China partner is sought for further development and, in our view, full ESLIM-01 data publication could be the catalyst for a licensing deal.

Scope and scale of registration trial programme is yet to be determined

The size and scope of a multi-regional Phase III clinical trial programme for sovleplenib in ≥2L adult ITP is yet to be determined, pending further interactions with regulators, and will likely also involve input from the future partner. Recent Phase III trials in ITP suggest a sample size of 150-200 patients and a 24-week double blind period with a subsequent open label extension. Both the fostamatinib (two 24-week Phase III studies FIT-1 and FIT-2 with an open label extension FIT-3, n=150) and rilzabrutinib (LUNA-3 Phase III study in n=194 adults and 30 adolescents, 24-week double-blind period followed by 28-week open label period, and a four-week safety follow-up) Phase III programmes were placebo-controlled. However, with Tavalisse already approved, a potential approval decision for relzabrutinib possible in 2025/6, and heterogeneity in standard of care between various geographies, there may be a question whether a placebo and/or active comparator arm is appropriate, and if so, which is the most relevant comparator.

A similar approach to fruquintinib is likely

We expect global ex-China sovleplenib regulatory filings to also be supported by data from the international bridging study and China ESLIM-01 trial, the same strategy employed with the FDA and EMA submissions for fruquintinib in advanced metastatic colorectal cancer.

Also at EHA (1): Proof of concept in wAIHA

wAIHA is an additional indication under development

China development of sovleplenib is underway in a second indication, warm antibody autoimmune hemolytic anemia (wAIHA). The first patient was dosed in the registration stage of the randomized, double-blind, placebo-controlled Phase II/III ESLIM-02 study during March 2024.

Currently a true orphan disease with no treatment approved

wAIHA is a rare acquired haemolytic autoimmune disorder with no current FDA approved treatment options, and significant morbidity and mortality. It is a form of anaemia which results from autoantibodies against erythrocyte surface antigens causing accelerated red blood cell destruction at body temperature (hence, 'warm'). wAIHA is the most prevalent form of AIHA, representing c 70% of cases.

A clear need for additional treatment options

As with ITP, corticosteroids are the gold standard 1L therapy, initially producing responses in c 80% of patients; although, again most patients relapse or become refractory to treatment. Despite its late onset of effect (after four to six weeks) and common occurrence of relapse, rituximab is also used off-label either 1L in combination with steroids or as 2L monotherapy. Immune suppressants (eg azathioprine, cyclosporine, mycophenolate) are used 3L, with splenectomy a later-stage treatment option in chronic drug-refractory cases.

Syk inhibition offers an attractive treatment rationale

Several novel agents are in development, including those that boost autoantibody clearance (eg Janssen's FcRn-targeting monoclonal antibody (mAb) nipocalimab in Phase II), and reduce autoantibody production (eg PI3Kδ inhibitor parsaclisib [Incyte] in Phase III). Others target B-cells via various different mechanisms of action such as mAbs targeting anti-BAFF (B-cell activating factor, eg ianalumab, Novartis, Phase III) or anti-D19/FcγRIIb (obelexelimab, Zenas BioPharma, Phase III), and small molecule kinase inhibitors like proteasome inhibitor bortezomib (Velcade), BTK inhibitor rilzabrutinib (Sanofi, Phase II), and Syk inhibitors fostamatinib (Phase III with open-label extension) and sovleplenib. The rationale for targeting Syk in wAIHA is two-fold: firstly, Syk inhibition blocks phagocytosis and destruction of red blood cells, and, secondly, it decreases B-cell activation reducing autoantibody production.

Promising data from ESLIM-02 Phase II study

Data from the Phase II part of the ESLIM-02 study were presented at EHA 2024. These results (Exhibit 6) showed a promising haemoglobin (Hb) improvement compared with placebo in 21 Chinese adults with wAIHA who had failed at least one prior line of corticosteroid therapy (median three lines of prior therapy) and a favourable safety profile. The primary endpoint was overall Hb response (at least one Hb ≥100 g/L with an increase of ≥20 g/L from baseline, not impacted by rescue therapy) within 24 weeks. The ORR was 43.8% for sovleplenib vs 0% for the placebo arm in the first eight weeks; with an ORR of 66.7% for sovleplenib at 24 weeks. The latter included patients who had crossed over from placebo into the 16-week open-label portion of the trial. We note that in eight patients who had previously received anti-CD20 therapy (ie rituximab) the ORR and DRR were 62.5% and 37.5%, respectively.

Exhibit 6: ESLIM-02 Phase II wAIHA efficacy analyses

Efficacy endpoints	Double-blind phase (0-8 weeks)		0-24 weeks
	Sovleplenib (n=16)	Placebo (n=5)	Overall (n=21)*
ORR %	43.8%	0%	66.7%
DRR %	18.8%	0%	47.6%
Rescue therapy use %	25%	60%	28.6%
TTR with Hb increase of ≥5g/L from baseline weeks median (range)	1.3 (0.9-5.9)	N/A	4.1 (0.9-22.1)

Source: HUTCHMED; EHA 2024 (presentation: S297) Note: DRR = durable response rate; ORR = overall response rate; TTR = time to response; * = includes five patients crossed over from placebo (for a 16-week open-label treatment period on sovleplenib)

Mixed results for fostamatinib in FORWARD Phase III trial

The first-in-class Syk inhibitor fostamatinib is currently in a Phase III open-label extension, which has enrolled 71 of the 90 patients that had completed the international Phase III FORWARD study. Results of FORWARD were mixed, with the primary endpoint of a durable response not met in the overall population due to a high placebo response in the Eastern European patients; however, a regional analysis (including the US, Canada, Australia, and Western Europe) showed a DRR of 32% with fostamatinib vs zero in the placebo arm (p=0.0021). No new safety

findings emerged, and the safety profile of fostamatinib was consistent with prior clinical experience with diarrhoea, fatigue, and hypertension the most common side effects. The Phase II fostamatinib wAIHA trial reported a DDR of 46%. Phase II results for Sanofi's BTK inhibitor rilzabrutinib, the next most advanced oral drug candidate in development for wAIHA, are expected in H224.

Also at EHA (2): initial Phase I data in HL

Encouraging initial Phase I sovleplenib data in heavily-pretreated Hodgkin's Lymphoma

We also note that HUTCHMED presented a poster at EHA with initial data from the dose expansion stage of the US/European Phase I lymphoma study. The data focused on the evaluation of sovleplenib in 25 heavily-pretreated (4L+) Hodgkin's Lymphoma patients, 92% of which had received ≥3 lines of prior therapy (eg a PD-1 checkpoint inhibitor and/or Pfizer/Seagen's Adcetris, brentuximab vedotin) with 44% having had an autologous stem cell transplant. The ORR was 25% in the 24 efficacy-evaluable patients at a median duration of follow up of 5.4 months, with two patients having a complete response (8.3%), four a partial response (16.7%). Ten patients had stable disease (41.7%). Median time-to-response was 1.9 months, with the median duration of response not yet reached.

The China ITP market opportunity for sovleplenib

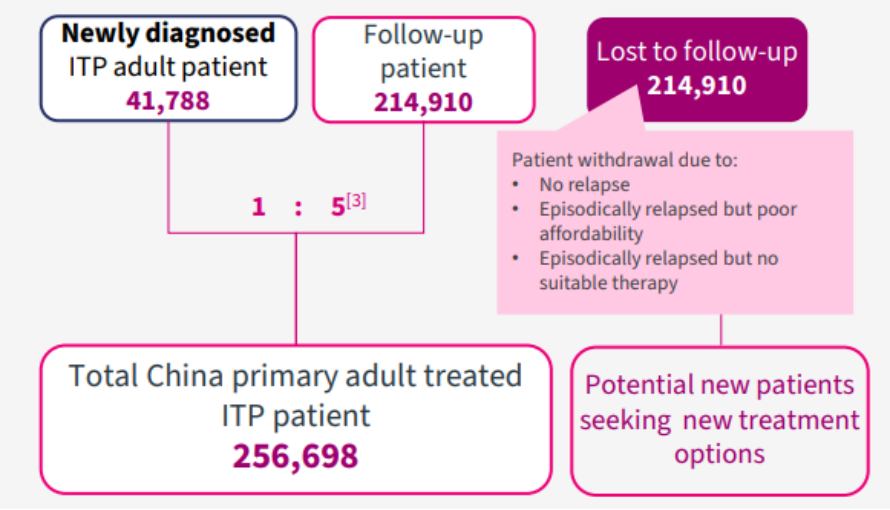
ITP market value set to shrink as key existing products face major patent expiries

According to Evaluate, the global ITP market stood at c $3.2bn in 2023 but is forecast to shrink by a 5.4% CAGR to $2.2bn in 2030, largely due to the impact of the two key existing TPO/TPO-RA therapies - Novartis's Promacta (eltrombopag: roughly half of total FY23 sales of $2.3m were in ITP) and Amgen's NPlate (romiplostim: FY23 sales of $1.4bn, largely in ITP) - going off patent in major markets in August 2027 and December 2028 (albeit earlier in Asia: March 2025) respectively. However, new treatment options are needed given both the heterogeneity of the disease and the limited efficacy, durability, and/or tolerability of conventional ITP therapies, which means that a large proportion of ITP patients relapse, or are lost to follow up, even after cycling through different treatment options over several years.

ITP incidence and prevalence is relatively low, but high clinical need means market is attractive

According to Blood 2017, the incidence of primary ITP in adults is 3.3 per 100k per year, with a prevalence of 9.5 per 100k adults. This, coupled, with relatively high five-year survival rates of 80% (Transfusions 2023) suggests that despite ITP's characterisation as a rare blood disease, the addressable patient population is still significant. Extrapolating from these figures, the prevalence of primary ITP in China is c 120k adult patients. However, an IQVIA survey for HUTCHMED indicates that China ITP prevalence is five-times higher than incidence (c 42k per year) which, when coupled to an additional pool of patients who are not in active treatment (seeking new treatment options due to relapse or becoming refractory, or due to affordability concerns), reveals an attractive China market opportunity in ITP (Exhibit 7). IQVIA analyses also suggest a 4% five-year CAGR in patient numbers over 2022-27.

Exhibit 7: China primary adult ITP patient size (2022, people)



Source: HUTCHMED Note: [3] = IQVIA analysis

Uncertainty for positioning, pricing, and treatment duration means conservative estimates

These analyses suggest an opportunity for sovleplenib in both the currently treated (c 250k patients of which c 67% on ≥2L, therapy) and untreated ITP patient segments (c 215k patients). As a reminder, in China, 2L ITP therapy is TPO/TPO-RA (following corticosteroids), and we highlight that around a quarter of the annual c $1.2bn in TPO sales in China relate to ITP (c $300m) with the rest connected to use in chemotherapy-induced anaemia. Peak sales potential for sovleplenib will be influenced by currently unknown pricing and real-world duration of treatment (clinical data currently extends to 24 weeks) as well as

differences in patient compliance and affordability (with likely variable levels of insurance coverage dependent on region). In our view, the market dynamics support an upgrade to our China peak sales assumption to $300m (from $200m), and following acceptance of the China NDA and presentation of detailed Phase III data we also increase our success probability in China to 95% (from 85%). In addition, given more visibility on plans for sovleplenib's first follow-on indication, wAIHA, an indication with similar patient dynamics to ITP and which can be addressed with the same commercial footprint, we ascribe a placeholder of $50m in China peak sales. With all else being equal, these changes result in a c 5% uplift to our overall HUTCHMED valuation.

Ex-China partner will influence global opportunity

Addressable patient market may be larger than originally thought

Outside China, there are several estimates for ITP epidemiology. Extrapolating from the incidence/prevalence data outlined above, there are c 50-60k adult patients living with ITP across the seven major markets, ie US, Japan, and EU5 (Germany, France, Italy, Spain, and UK). However, other sources put this figure higher at up to c 200k adults. Epidemiological analyses and market research carried out by Sanofi to support its BTK inhibitor rilzabrutinib identifies a total ITP market of c 210k in the US, EU5 and Japan, with c 50k patient eligible for ≥2L therapies (December 2023 R&D day); while Rigel's analysis of the US ITP market for fostamatinib indicates 81.3k adult ITP patients of which 44.3k are actively treated and c 24k are 2L or later (May 2024 presentation). We note the consistency in estimates that of the total diagnosed adult ITP population around half are currently treated, with around 50% of those treated (ie c 25% of those diagnosed) eligible for 2L therapy.

Perceived quality of the partner could be a major determinant of commercial uptake

The ITP treatment paradigm in key global markets is different to China. While TPO/TPO-RA is a mainstay of 2L therapy, there are a plethora of options used in subsequent lines of therapy, including off-label or in novel combinations. These different later lines (including non-responders, refractory patients, and those not tolerating treatment) could all represent a potential opportunity for sovleplenib to capture patients. At this stage, we believe that the reach and reputation of the future ex-China global partner will have the greatest bearing on the market opportunity for sovleplenib. Assessing peak sales potential is complicated by several factors including the current lack of visibility on potential pricing, likely levels of reimbursement coverage and, in the US, the formulary status needed to drive uptake.

Rigel's Tavalisse has forecast peak sales of $203m, Sanofi's rizlabrutinib of $422m

For context, we note that Rigel's Tavalisse posted FY23 sales of $93.7m, with Evaluate consensus indicating peak sales of $203m in 2030, $161m of which relates to the US. Assuming a positive approval decision, Sanofi's rilzabrutinib could launch in 2025, and according to Evaluate, has consensus peak sales of $422m in 2030.

Exhibit 8: Summary of financials

Year-end: December 31	$'000s	2021	2022	2023	2024E	2025E
INCOME STATEMENT						
Revenues		**356,128**	**426,409**	**837,999**	**611,687**	**771,257**
Cost of goods sold		(258,234)	(311,103)	(384,447)	(377,439)	(422,501)
Gross Profit		**97,894**	**115,306**	**453,552**	**234,248**	**348,756**
R&D expenses		(299,086)	(386,893)	(302,001)	(279,716)	(250,683)
Selling expenses		(37,827)	(43,933)	(53,392)	(61,319)	(69,001)
G&A expenses		(89,298)	(92,173)	(79,784)	(82,178)	(84,643)
Underlying operating profit		**(328,317)**	**(407,693)**	**18,375**	**(188,966)**	**(55,571)**
Other revenue/expenses		0	0	0	0	0
EBITDA		**(321,127)**	**(399,029)**	**26,582**	**(179,581)**	**(45,446)**
Operating Profit		**(328,317)**	**(407,693)**	**18,375**	**(188,966)**	**(55,571)**
Interest income/expense		1,484	8,947	35,386	24,028	14,976
Other income/expense		(10,217)	(11,676)	4,547	(3,000)	0
Profit Before Taxes		**(215,740)**	**(410,422)**	**58,308**	**(167,938)**	**(40,595)**
Adj. PBT		**(337,050)**	**(410,422)**	**58,308**	**(167,938)**	**(40,595)**
Current tax income		(11,918)	283	(4,509)	(2,681)	(2,840)
Equity in earnings of equity investees, net of tax		60,617	49,753	47,295	50,118	52,624
Net Income		**(167,041)**	**(360,386)**	**101,094**	**(120,501)**	**9,189**
Minority interests		(27,607)	(449)	(314)	(330)	(346)
Net income attributable to equityholders		**(194,648)**	**(360,835)**	**100,780**	**(120,831)**	**8,843**
EPS ($)		**(0.25)**	**(0.43)**	**0.12**	**(0.14)**	**0.01**
Earnings per ADS ($)		**(1.23)**	**(2.13)**	**0.59**	**(0.71)**	**0.05**
DPS ($)		**0.00**	**0.00**	**0.00**	**0.00**	**0.00**
Average no. of shares (m)		792.7	847.1	849.7	853.9	854.4
Gross margin		*27%*	*27%*	*54%*	*38%*	*45%*
EBITDA margin		*N/A*	*N/A*	*3%*	*N/A*	*N/A*
Underlying operating margin		*N/A*	*N/A*	*2%*	*N/A*	*N/A*
BALANCE SHEET						
Current assets		**1,212,076**	**839,888**	**1,096,839**	**994,939**	**1,058,274**
Cash and cash equivalents		377,542	313,278	283,589	355,090	746,367
Short-term investments		634,158	317,718	602,747	402,747	0
Accounts receivable		83,580	97,988	116,894	134,068	190,173
Inventories		35,755	56,690	50,258	59,683	78,383
Other current assets		81,041	54,214	43,351	43,351	43,351
Non-current assets		**160,585**	**189,557**	**182,934**	**144,126**	**97,356**
Property, plant & equipment		41,275	75,947	99,727	105,363	105,238
Intangible assets		3,543	3,222	3,085	3,064	3,064
Investments in equity investees		76,479	73,777	48,411	3,988	(42,657)
Other non-current assets		39,288	36,611	31,711	31,711	31,711
Current liabilities		**(311,658)**	**(353,903)**	**(403,027)**	**(395,170)**	**(393,682)**
Short-term debt		(26,905)	0	(31,155)	(31,155)	(31,155)
Accounts payable		(41,177)	(71,115)	(36,327)	(46,547)	(55,139)
Other current liabilities		(243,576)	(282,788)	(335,545)	(317,468)	(307,388)
Non-current liabilities		**(21,489)**	**(38,672)**	**(133,359)**	**(88,273)**	**(62,765)**
Long-term debt		0	(18,104)	(48,189)	(46,593)	(44,997)
Other non-current liabilities		(21,489)	(20,568)	(85,170)	(41,680)	(17,768)
Equity		**1,039,514**	**636,870**	**743,387**	**655,622**	**699,183**
CASH FLOW STATEMENTS						
Operating cash flow		**(204,223)**	**(268,599)**	**219,258**	**(152,400)**	**(45,326)**
Net income		(167,041)	(360,386)	101,094	(120,501)	9,189
Non-cash adj & other operating cash flow		(69,640)	33,083	47,018	42,120	44,497
Change in working capital		32,458	58,704	71,146	(74,019)	(99,013)
Investing cash flow		**(306,320)**	**296,588**	**(291,136)**	**229,423**	**439,392**
CAPEX		(16,401)	(36,664)	(32,612)	(15,000)	(10,000)
Change in short term investments		(434,612)	316,440	(285,029)	200,000	402,747
Investment in an equity investee		144,693	16,812	29,495	44,423	46,645
Financing cash flow		**650,028**	**(82,763)**	**48,660**	**(5,523)**	**(2,788)**
Proceeds from equity		660,501	(47,993)	(3,977)	(0)	(0)
Increase in loans		0	(9,170)	61,705	(1,596)	(1,596)
Other financing cash flow		(10,473)	(25,600)	(9,068)	(3,927)	(1,192)
Net increase in cash		**139,485**	**(54,774)**	**(23,218)**	**71,501**	**391,277**
Exchange rate effects		2,427	(9,490)	(6,471)	0	0
Cash at start of year		235,630	377,542	313,278	283,589	355,090
Cash at end of year		**377,542**	**313,278**	**283,589**	**355,090**	**746,367**
Net cash at end of year		**984,795**	**612,892**	**806,992**	**680,089**	**670,215**

Source: Company, Trinity Delta Note: Adjusted PBT excludes exceptionals, Cash includes short-term investments

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