The information contained within this announcement is deemed by the Group to constitute inside information as stipulated under the Market Abuse Regulation (EU) No. 596/2014. Upon the publication of this announcement via the Regulatory Information Service, this inside information is now considered to be in the public domain

Shield Therapeutics plc
("Shield" or the "Group" or the "Company")

AEGIS-H2H study update

London, UK, 17 March 2020: Shield Therapeutics plc (LSE: STX), a commercial stage, pharmaceutical company with a focus on addressing iron deficiency with its lead product Feraccru®/Accrufer® (ferric maltol), a novel oral iron treatment, today provides an update and clarification relating to the AEGIS-H2H clinical trial, the data from which was primarily designed to be used in health economic analyses, pricing and reimbursement applications as well as marketing purposes.

This update has no impact on existing marketing authorisations in the EU, US and Switzerland, nor on any approved prescribing information and the data from this AEGIS-H2H study has not been used in any of the regulatory submissions that have led to the approval of Feraccru®/Accrufer® in either Europe, the USA or Switzerland.

Based on a range of positive clinical trials Feraccru®/Accrufer® is approved for the treatment of iron deficiency in adults with or without anaemia in the USA, the European Union and Switzerland. Commercial partners including Norgine BV and Beijing Aosaikang Pharmaceutical Co. Ltd have licensed the rights to Feraccru®/Accrufer® in the European Union, Australia, New Zealand and China and a partnering process for the commercial rights to Feraccru®/Accrufer® in the USA is also currently being conducted with the Company continuing to work diligently towards the appointment of a suitable commercial partner.

On 4 March 2019 Shield announced that the AEGIS-H2H clinical trial had delivered positive results, demonstrating that Feraccru®/Accrufer® is non-inferior to a market-leading intravenous (IV) iron therapy in treating iron deficiency anaemia in adults with inflammatory bowel disease (IBD). The announcement stated that primary analysis of the AEGIS-H2H study demonstrated the response to Feraccru®/Accrufer® at 12 weeks was within 9% of the response seen with the IV iron therapy and within the 20% limit required by the study protocol to confirm non-inferiority ($p = 0.022$, subsequently adjusted to $p = 0.017$ after detailed analysis).

The above statement was made in relation to the "per protocol" (PP) analysis of the study results. These data have been published and presented at both the United European Gastroenterology Week (UEGW)[1] and European Crohn's and Colitis Organisation (ECCO)[2] scientific congresses. The PP analysis refers to those patients who fully complied with the study design and remained on the study for the full 12-week period, at the end of which the primary end point was measured. With an open-label design, as was used in this study, the true efficacy of the different oral and intravenous treatment arms is better determined by using the PP population, which accounts for low compliance and early withdrawal, whereas the "intention to treat" (ITT) population is liable to overestimate the adverse events and underestimate the efficacy of the oral agent as these are given via daily administration, whereas the comparator is administered as a bolus dose. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) advises caution in the use of ITT analyses in non-inferiority trials[3]. Therefore, it was decided to use the PP population for the primary efficacy analysis.

However, the pre-defined success criteria of this clinical study, as set out in the statistical analysis plan, inadvertently required that ferric maltol could be considered non-inferior to IV iron if the difference in the proportion of responders in each arm at week 12 was less than 20% in <u>both</u> the ITT and the PP analyses, but should have allowed for non-inferiority if <u>either</u> the PP or ITT populations achieved this target. In the ITT analysis (which refers to all patients who were randomised into the study, whether or not they completed the entire 12-week

period and fully complied with the study design), Feraccru®/Accrufer® clearly demonstrated effectiveness, but did not achieve non-inferiority compared to the IV iron therapy. The 4 March 2019 announcement should therefore have made it clear that the study did not achieve non-inferiority in both of the ITT and PP analyses.

In light of the above finding which has just come to light, the Board has instigated an immediate independent review into the analysis of both datasets, which is being overseen by a non-executive director. The Company will update the market on this review in due course.

As stated above, this clarification has no impact on existing marketing authorisations, nor on any approved prescribing information and the data was not used in the regulatory submissions that led to the approval of Feraccru®/Accrufer® in either Europe, the USA or Switzerland. Shield remains confident that data from the AEGIS-H2H study including the long term extension results, together with the existing positive efficacy and safety data on the product provide compelling evidence that Feraccru®/Accrufer® is an important treatment alternative for many patients, combining efficacy with good tolerability, without the need for hospital administration.

In the meantime, the Company is working closely with its commercial partners to ensure relevant information is clearly communicated to all stakeholders in a timely manner.

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About Shield Therapeutics plc

Shield is a de-risked, commercial stage, specialty pharmaceutical company delivering innovative pharmaceuticals to address patients' unmet medical needs. The Company's clear purpose is to develop products that help patients become people again, enabling them to enjoy the things that make a difference in their everyday lives. The Group's lead product, Feraccru®/ Accrufer® has exclusive IP rights until the mid-2030s and is approved for the treatment of iron deficiency with or without anaemia in adults in the European Union, the United States and Switzerland. In Europe it is marketed as Feraccru® with commercialisation led by Norgine BV and in the USA the product will be marketed as Accrufer® with Shield currently in the process of selecting a commercialisation partner. Shield also has an exclusive licence agreement with Beijing Aosaikang Pharmaceutical Co. Ltd for the development and commercialisation of Feraccru®/Accrufer® in China, Hong Kong, Macau and Taiwan. For more information please visit www.shieldtherapeutics.com

About Feraccru®/Accrufer®

Feraccru®/Accrufer® is a novel, stable, non-salt based oral therapy for adults with iron deficiency with or without anaemia that has been shown to be an efficacious and well-tolerated therapy in a range of controlled phase 3 trials,

and offers a compelling alternative to IV iron for those patients unable to tolerate salt-based oral iron therapies and wish to avoid the complexities of infusion-based iron therapies.

When salt-based oral iron therapies are ingested they can cause a range of mild-to-severe gastrointestinal tract (GI) adverse events, including nausea, bloating and constipation through the release and subsequent reactivity of free iron in the GI tract, leading to poor tolerability, reduced patient compliance and ultimately treatment failure. Feraccru®/Accrufer® is not an iron salt and, as a result, it does not routinely cause the same treatment-limiting intolerance issues of salt-based iron therapies, whilst the iron from the ferric maltol molecule can be readily absorbed.

Prior to Feraccru®/Accrufer®, IV iron therapies were the only realistic alternative treatment option for iron deficient patients with or without anaemia intolerant of or unwilling to be treated salt-based oral iron therapies. However, use of such an invasive, costly, inconvenient and complex to administer treatment option, which is associated with potentially life-threatening and spontaneous hypersensitivity reactions, means there remains a clear unmet medical need for these patients to have access to an effective therapy that is well tolerated, convenient and does not require hospital-based administration. Feraccru®/Accrufer® meets those requirements.

About Iron Deficiency

The WHO states that iron deficiency is the most common and widespread nutritional disorder in the world. As well as affecting a large number of women and children in non-industrialized countries, it is the only nutrient deficiency which is also significantly prevalent in virtually all industrialised nations. There are no current global figures for iron deficiency but, using anaemia as an indirect indicator, it can be estimated that most preschool children and pregnant women in non-industrialised countries, together with at least 30-40% in industrialized countries, are iron deficient.

Footnotes

1. Howaldt S *et al.* OP195. UEG Journal. 2019 Vol. 7(8S):106 Doi:10.1177/2050640619854663
2. Howaldt S, et al. P685, presented at ECCO 2020; Howaldt S, et al. P331, presented at ECCO 2020, Howaldt S, et al. P567, presented at ECCO 2020
3. European Medicines Agency. ICH Topic E 9 Statistical Principles for Clinical Trials. CPMP/ICH/363/96. September 1998.