**CLINICAL STUDY PROTOCOL**

# A Phase 3, Randomized, Placebo Controlled, Prospective, Multicenter Study with Oral Ferric Maltol for the Treatment of Iron Deficiency Anemia in Subjects with Chronic Kidney Disease.

**Protocol Number:** ST10-01-303

**Test Drug:** Ferric Maltol (ST10)

**IND Number:** 114832

**Study Name:** AEGIS CKD

**Sponsor:** Shield TX (UK) Limited
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**(Note:** Only change from Version 2.0 is formatting of Section 9.2)

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## 2 ABBREVIATION INDEX

| | |
|---|---|
| AE | Adverse Event |
| ALT | Alanine Aminotransferase |
| ANCOVA | Analysis of Covariance |
| AST | Aspartate Aminotransferase |
| AUC | Area Under the Plasma Concentration Curve |
| Bid | Twice Daily |
| C | Celsius |
| CHr | Reticulocyte Hemoglobin Concentration |
| CKD | Chronic Kidney Disease |
| CMAX | Maximum Plasma Concentration |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CRP | C-Reactive Protein |
| CS | Clinically Significant |
| CSR | Clinical Study Report |
| EC | Ethics Committee |
| ECG | Electrocardiogram |
| eGFR | Estimated Glomerular Filtration Rate |
| ESA | Erythropoiesis Stimulating Agent |
| FDA | US Food and Drug Administration |
| GCP | Good Clinical Practice |
| GGT | Gamma-Glutamyl Transpeptidase |
| GI | Gastrointestinal |
| GMP | Good Manufacturing Practice |
| h | Hour |
| Hb | Hemoglobin |
| IBD | Inflammatory Bowel Disease |
| ICH | International Conference on Harmonization |
| ID | Iron Deficiency |
| IDA | Iron Deficiency Anemia |
| IMP | Investigational Medical Product |
| IRB | Institutional Review Board |
| ITT | Intention-To-Treat |
| IV | Intravenous |
| IXRS | Interactive Tel/Web Response System |
| KDGIO | Kidney Disease Improving Global Outcomes Organization |
| LOCF | Last Observation Carried Forward |
| MCH | Mean Corpuscular Hemoglobin |
| MCHC | Mean Corpuscular Hemoglobin Concentration |
| MCV | Mean Cell Volume |
| MDRD | Modified Diet in Renal Disease |
| MMRM | Mixed Model Repeat Measures |
| NCS | Non-Clinically Significant |

| | |
|---|---|
| ND-CKD | Non Dialysis Dependent Chronic Kidney Disease |
| OFP | Oral Ferrous Product |
| PHI | Protected Health Information |
| PK | Pharmacokinetics |
| PP | Per Protocol |
| PR | Electrocardiogram PR Interval |
| QRS | Electrocardiogram QRS Interval |
| QT | Electrocardiogram QT Interval |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SPC | Summary of Product Characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| T1/2term | Terminal Half-life |
| TMAX | Time to Maximum Plasma Concentration |
| TSAT | Transferrin Saturation |
| UC | Ulcerative Colitis |
| WHO | World Health Organization |

## 3 SYNOPSIS

**Title** A phase 3, randomized, placebo controlled, prospective, multicenter study with oral ferric maltol for the treatment of iron deficiency anemia in subjects with chronic kidney disease.

**Protocol Number** ST10-01-303

**Study Name** AEGIS CKD

**Test Drug** Ferric maltol (ST10)

**Comparator** Placebo

**Phase** Phase 3

**Sites** Approximately 35 sites

**Study Rationale** The existing scientific and clinical experience with ferric maltol in the treatment of iron deficiency anemia (IDA) in patients with inflammatory bowel disorder (IBD) supports further investigation into the treatment of IDA with ferric maltol due to other causes. The need for improved management of IDA in patients with chronic kidney disease (CKD) is well established and ferric maltol could provide an effective and well-tolerated oral treatment for CKD patients as an alternative to oral ferrous products (which are often poorly tolerated and hence ineffective) and to intravenous (IV) iron administration (which may be inconvenient and is associated with risk of allergic reaction or iron overload).

**Objectives**

**Primary Objective**

To evaluate the efficacy of oral ferric maltol compared with placebo in the treatment of IDA in subjects with CKD at 16 weeks.

**Secondary Objectives**

To evaluate the efficacy, safety, tolerability and pharmacokinetics of ferric maltol in subject with IDA and CKD over a treatment duration of up to 52 weeks.

**Endpoints**

**Primary Endpoint**

Change in Hb concentration from baseline to Week 16.

**Secondary Endpoints**

- Proportion of subjects that achieve an increase in Hb concentration of ≥1 g/dL at Week 16.
- Proportion of subjects that achieve a Hb concentration of ≥11 g/dL at week 16.
- Change in Hb concentration from baseline to Week 8.
- Proportion of subjects that achieve an increase in Hb concentration of ≥2 g/dL at Week 16.
- Change in Hb concentration from baseline to Week 4.
- Changes in iron parameters (ferritin, TSAT, serum iron).
- AEs/SAEs

**Pharmacokinetic (PK) Endpoints**

Population based PK analysis of maltol, maltol glucuronide and serum iron.

**Exploratory Endpoints**

Proportion of subjects with a baseline Hb of <10 g/dL that achieve a Hb > 10g/dL.

**Design**

- Screening: Up to 14 days
- Randomized, Double-Blind Treatment: 16 weeks treatment with oral ferric maltol, 30 mg capsule twice daily (bid) or oral matching placebo bid. Randomization will occur at a ratio of 2:1, ferric maltol to placebo.
- Open-label Treatment: Up to 36 weeks treatment with ferric maltol.
- End of Study: Week 52 or premature discontinuation.
- Post-treatment safety follow-up: 14 days following discontinuation of study medication.

Subjects that develop a ≥0.5g/dL decrease from baseline in Hb that falls below 8.0g/dL on 2 consecutive weeks will be discontinued from study treatment.

Subjects who discontinue from study treatment prior to Week 16 will be encouraged to continue with study visits and assessments up to and including assessments at week 16.

**Number of Subjects**

Approximately 168 subjects.

**Inclusion Criteria**

All of the following criteria must be met to randomize a subject in the study:

1. Ability to understand the information given in the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved information sheet and consent form. Must sign and date the informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations prior to any study mandated procedure.
2. Willing and able to comply with study requirements.
3. Age ≥ 18 years at the time of informed consent.
4. A current diagnosis of CKD with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m$^2$ and ≥15 mL/min/1.73m$^2$, as calculated using the abbreviated version of the Modified Diet in Renal Disease equation (MDRD) assessed via screening laboratory results.
5. Iron deficiency anemia defined by the following criteria assessed via screening laboratory results:
    a. Hb <11.0g/dL and ≥8.0g/dL
    b. AND ferritin <250ng/mL with a Transferrin saturation (TSAT) <25% OR ferritin <500ng/mL with a TSAT of <15%
6. Female subjects of childbearing potential (including perimenopausal females who have had a menstrual period within 1 year prior to screening) must agree to use a reliable method of contraception until study completion

and for at least 4 weeks following their final study visit. Reliable contraception is defined as a method which results in a low failure rate, i.e., less than 1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), complete sexual abstinence, a vasectomized partner and oral contraceptive medications. Female subjects who are surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or postmenopausal (defined as no menstrual period within 1 year of screening) are also allowed to participate.

**Exclusion Criteria** A subject who meets any of the following criteria is not eligible for participation in the study.

1. Anemia due to any cause other than iron deficiency, including, but not limited to:
    a. Untreated or untreatable severe malabsorption syndrome.
    b. Myelosuppression use (permitted if taken at a stable dose and frequency for at least 12 weeks prior to randomization and are expected to stay stable throughout the double-blind treatment period so long as there is no clinical evidence of the myelosuppression contributing to the subject's anemia).
2. Administration with any of the following prior to randomization:
    a. IV iron injection within the previous 4 weeks or administration of intramuscular or depot iron preparation within the previous 12 weeks.
    b. Single agent oral iron supplementation, taken specifically to treat anemia (e.g. ferrous sulfate, fumarate and gluconate) within the previous 2 weeks. Multivitamins are permitted.
    c. Use if ferric citrate and sucroferric oxyhydroxide within the previous 1 week.
    d. ESAs within the previous 4 weeks
    e. Blood transfusion or donation within the previous 12 weeks.
    f. Dimercaprol or cloramphenicol within the previous 7 days.
    g. Current use of methyldopa.
3. Currently receiving dialysis or initiation of dialysis is considered likely during the study.
4. Renal transplant within 12 months prior to randomization or is considered likely during the study.
5. Known hypersensitivity or allergy to the active substance or excipients of ferric maltol or placebo capsules.
6. Contraindication for treatment with iron preparations, e.g. hemochromatosis, chronic hemolytic disease, sideroblastic anemia, thalassemia, or lead intoxication induced anemia.
7. Impaired liver function as indicated by alanine aminotransferase (ALT) or aspartate transaminase (AST) > 3 times the upper limit of normal as assessed

via screening laboratory results.

8. Clinically significant vitamin B12 or folic acid deficiency as determined by the screening laboratory results (retest following at least 2 weeks of starting treatment with vitamin B12 or folate replacement is permitted).
9. Pregnant or breast feeding.
10. Concomitant medical conditions with significant active bleeding likely to initiate or prolong anemia; for example coagulation disorders or recurrent GI bleeding.
11. Scheduled or expected major surgery during the course of the study. (Minor surgeries not associated with significant blood loss, in the Investigator's judgement, are permitted e.g. surgery related to fistulae or vascular access, minor dental extractions, incision and drainage of abscess or simple excisions).
12. Participation in any other interventional clinical study within 30 days prior to screening.
13. Cardiovascular, liver, renal, hematologic, psychiatric, neurologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject and/or efficacy of the study drug or severely limit the lifespan of the subject.
14. Any other unspecified reason that, in the opinion of the Investigator or the Sponsor make the subject unsuitable for enrolment.

**Concomitant Medication**

**Not Permitted**

- IV iron injections, intramuscular or depot iron administrations.
- Single agent oral iron supplementation, taken specifically to treat anemia (e.g. ferrous sulfate, fumarate and gluconate).
- Ferric citrate or sucroferric oxyhydroxide.
- ESAs.
- Blood transfusions or donations.
- Dimercaprol, chloramphenicol or methyldopa

**Permitted**

- Myelosuppressants taken at a stable dose and frequency (so long as there is no clinical evidence of the myelosuppressant contributing to the subject's anemia).
- Multivitamins containing iron.

**Withdrawal Criteria**

- Withdrawal of informed consent.
- Unwillingness or inability to comply with protocol requirements.
- Pregnancy or not using a reliable method of birth control if female of childbearing potential.
- A ≥0.5g/dL decrease from baseline in Hb that falls below 8.0g/dL on 2

consecutive weeks.

- Ferritin >700ng/mL with a TSAT of >50% sustained for 2 consecutive weeks.
- SAEs that are judged by the Investigator to be related to study drug.
- Use of prohibited concomitant medications.
- Initiation of dialysis.
- Blood transfusions or donations for any cause.
- Any dose or frequency changes to myelosuppressants during the double-blind treatment period.
- Requirement for major surgery. Minor surgeries not associated with significant blood loss, in the Investigator's judgement, are permitted (e.g. surgery related to fistulae or vascular access, minor dental extractions, incision and drainage of abscess or simple excisions).

Subjects who discontinue study treatment prior to Week 16 will be encouraged to continue with study visits and assessments up to and including assessments at week 16.

**Investigational Medicinal Product**

Ferric maltol, 30 mg capsules or matching placebo twice daily. To be taken orally first thing in the morning before breakfast and last thing at night before bed. Capsules must be taken on an empty stomach with water only.

**Statistical Methods**

**Sample size calculation**

A sample size of 135 subjects (Randomized 2:1, ferric maltol:Placebo, 90 in the ferric maltol group and 45 placebo) will have 95% power to detect a statistically significant treatment difference of 1.0g/dL between ferric maltol and placebo on the primary endpoint, using a two-sided 0.05 significance level. This calculation assumes a common standard deviation of 1.5g/dl which is based on a pooled estimate of SDs obtained from published trials. Assuming a drop-out rate of 20%, approximately 168 subjects total will be recruited. Subjects will be stratified based on baseline Hb value and eGFR.

**Statistical Methods**

An Analysis of Covariance (ANCOVA) will be used to analyse the primary endpoint: change in Hb concentration from baseline to Week 16. Missing change from baseline hemoglobin concentration data for week 16 will be imputed using multiple imputation methodology. This will generate 10 complete datasets containing imputed values for those missing in the original dataset. Hb concentrations at baseline, Week 4, Week 8 and gender will be considered as variables helpful in guiding this imputation. For each imputed dataset, the change from baseline to Week 16 complete datasets will be analysed using analysis of covariance (ANCOVA) with factors for treatment and disease and a covariate of baseline hemoglobin and eGFR. By combining the results from these analyses, the treatment estimates will be constructed using the parameter estimates and associated standard errors. Similarly the difference of the adjusted treatment means (ferric maltol – placebo) will be presented with the associated standard error and 2-sided 95 % confidence interval. The primary endpoint analysis will be performed using the intention-to-treat (ITT) population.

# 4 BACKGROUND INFORMATION

## 4.1 OVERVIEW OF DISEASE

IDA is commonly associated with chronic kidney disease (CKD) and it is one of the leading causes of morbidity and mortality (Regidor 2006; Hsu 2002). It is appropriate to administer regular iron replacement therapy as part of standard medical care Post 2006; KDOQI 2006). IDA can be due to multiple factors, most significantly lack of production of erythropoietin, blood loss through gastrointestinal (GI) bleeding, medical procedures and/or impaired dietary iron absorption (Lopez 2015). In some patients there may be an inflammatory component to their CKD, and chronic inflammation can make absorption and utilization of iron less efficient compared to the normal state (Zaritsky 2009). Anemia can be found in CKD patients receiving dialysis and also in non-dialysis dependent CKD (ND-CKD) patients (Gotloib 2006; Post 2006). IDA is defined by lower than normal hemoglobin (Hb), ferritin and transferrin-saturation (TSAT) levels (KDOQI 2006).

The incidence of anemia varies with the severity or stage of CKD; the percentage of patients with haemoglobin ≤ 12 g/dL increases from 26.7% to 75.5% when glomerular filtration rate decreases from ≥ 60 mL/min/1.73 m2 to < 15 mL/min/1.73 m2. Prevalence of haemoglobin ≤ 10 g/dL increases substantially from 5.2% to 27.2% when glomerular filtration rate diminishes from ≥ 60 mL/min/1.73 m2 to < 15 mL/min/1.73 $m^2$ (Hsu 2002; McClellan 2004; Stauffer 2014). The use of erythropoiesis stimulating agents (ESAs) has made significant improvements to managing anemia in CKD. However excessive use is associated with cardiovascular events and increased mortality (KDOQI 2006) such that the US Food and Drug Administration (FDA) has issued revised guidance on their use (FDA 2011). The importance of ESA use in combination with correction of ID is well-recognized, enabling anemia correction with lower doses of ESAs (Fishbane 1997; KDOQI 2006).

Replacement of iron stores with oral ferrous iron can be affected by non-adherence to the prescribed course of medication due to the incidence and severity of GI side effects in patients with CKD (Charytan 2005; Macdougall 1999; Horl 2007). Moreover, in CKD, there may be reduced absorption of ferrous iron associated with inflammation (Ganz 2003). IV iron or oral iron is recommended for non-dialysis CKD patients (KDOQI 2006) but IV iron administration when treatment with oral ferrous products is ineffective or not tolerated (KIDGO 2012; Lopez 2015). However IV iron administration is not subject to normal gut physiological control mechanisms of iron absorption and depletion, and therefore iron overload is a potential risk (Vecchio 2016; Horl 2007). Infused or IV push iron products are associated with a small but significant risk of infusion reactions, and administration requires appropriate resuscitation equipment and staff to be on hand (KDOQI 2006). While this may not be an issue in hemodialysis clinics for those patients on home dialysis, peritoneal or hemodialysis, IV iron requires a hospital or clinic visit which may be inconvenient to patients/carers and is costly (Bhandari 2011).

In consideration of the above, an effective and tolerable oral iron replacement therapy would be a significant improvement to the care of ND-CKD and home dialyzed patients as an alternative to IV irons or poorly tolerated OFPs.

## 4.2 CURRENT TREATMENT OF DISEASE

CKD management guidelines, Kidney Disease Outcomes Quality Initiative (KDOQI 2006) specify iron replacement therapy is indicated to target a Hb level of 11 g/dL or greater, a serum ferritin of greater than 100 ng/mL and a TSAT of greater than 20% and that the route can be either IV administration or oral. The Kidney Disease Improving Global Outcomes (KIDGO 2012) guidelines

recommend, for ND-CKD patients, an initial 1-3 month trial of oral iron therapy or, alternatively, IV iron based on severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance and cost.

Oral iron, ferrous sulfate, is available in multiple formulations and dosages, but is typically taken as 200 mg tablets (65 mg elemental iron) 2 to 3 times daily (ferrous sulfate patient information leaflet 2015). However, as the duodenum can maximally absorb only 10-20 mg of iron a day, greater than 90% of ingested iron is not absorbed, leading to symptomatic adverse events (AEs) including potential mucosal erosions and enteric siderosis (Zhu, 2010). Common adverse effects of oral iron supplements include nausea, epigastric discomfort, and constipation, all of which appear dose-related. Adverse effects can occur in up to 20% of subjects, significantly impairing compliance and rendering the treatment ineffective (Zhu, 2010).

### 4.3 OVERVIEW OF TEST PRODUCT

In an effort to overcome the significant challenges of iron substitution with oral ferrous products (OFP), ferric maltol, a chemically stable complex formed between ferric iron (Fe3+) and maltol (3-hydroxy-2-methyl-4-pyrone) was developed. Ferric maltol makes iron available in the GI tract, providing the iron in a biologically labile form for uptake onto transferrin and ferritin and ultimately haematopoiesis and storage on ferritin. European Commission marketing authorization was granted for ferric maltol in February 2016.

Unlike OFPs, which are often given with food in order to reduce side effects, ferric maltol can, and should, be given on an empty stomach to maximise bioavailability. Oral ferric iron chelated with maltol can be administered with improved tolerability and the total dose exposure of unabsorbed iron within the GI tract is significantly reduced.

In early human studies, maltol was not detected in the systemic circulation following oral intake of ferric maltol. This suggests that following absorption, maltol undergoes rapid and complete first pass metabolism, is bio transformed to maltol-glucuronide, and excreted in the urine. This is consistent with the known metabolism and excretion of maltol absorbed naturally from the diet (WHO 2006; Barrand 1991).

### 4.4 DOSE SELECTION AND RESULTS OF PREVIOUS CLINICAL STUDIES

Ferric maltol is not absorbed systemically as an intact complex and traditional PK studies may not provide the relevant information (Barrand 1991). Therefore, a model was developed to determine the optimal dose. Data from 6 previous studies of ferric maltol in subject with IBD and IDA were used to estimate absorption rates in the study population. Using these data, the model suggested that in a compliant study population, 30 mg ferric maltol bid would result in correction of baseline anemia in the majority of subjects.

An open-label, randomized Phase 1 study evaluated the pharmacokinetics of ferric maltol and its effect on iron indices in IBD patients with iron deficiency (with or without anemia). Twenty four subjects received ferric maltol 30, 60, or 90 mg bid over an 8-day period. Pharmacokinetics and iron uptake were assessed on Days 1 and 8. Ferric maltol showed predictable pharmacokinetics, with linear increases in exposure, no accumulation over 7 days, and improvements in iron uptake across the dose range 30–90 mg bid.

The dose chosen for Phase 3 studies is 30 mg bid ferric maltol, or 60 mg elemental iron total daily dose.

A Phase 3 study has been completed in subjects with IDA and Inflammatory Bowel Disease (IBD), who are intolerant of oral iron products or are unsuitable for treatment with them (ST10-01-301 and ST10-01-302; Gasche 2014). 128 subjects were randomized to 12 weeks of blinded medication (30mg bid ferric maltol or matched placebo capsule) followed by a 52 week open-label extension period; during which all available subjects received ferric maltol at the same dose. 87% and 82% ferric maltol and placebo treated subjects, respectively, completed the 12 week double blind period. The difference between the treatment groups in mean Hb from baseline to week 12 was 2.25g/dL (ANCOVA p<0.0001). Hb increased to normal values at week 12 in 65% of ferric maltol group and 10% of placebo subjects. When the placebo subjects were transferred to ferric maltol treatment in the open-label phase, there was a sharp rise in Hb levels that mirrored the response in the ferric maltol group in the double-blind phase. There were further increases in Hb up to 48 weeks of treatment and no indication of any reduction in efficacy over the full 64 week treatment period.

Refer to the Investigator Brochure for further information.

## 4.5 RATIONALE FOR THE STUDY

Clinical studies conducted to date provide evidence for the therapeutic potential of ferric maltol in patients with IDA in inflammatory bowel disease and other causes of IDA. A Phase 3 study in 128 subjects with IDA and IBD, who are intolerant of OFPs or are unsuitable for treatment with them (ST10-01-301 and ST10-01-302; Gasche 2014) demonstrated ferric maltol to be effective and well-tolerated.

The existing scientific and clinical experience with ferric maltol in the treatment of IDA in patients with inflammatory bowel disorder (IBD) supports its further investigation in the treatment of IDA due to other causes. The need for improved management of IDA in patients with chronic kidney disease (CKD) is well established and ferric maltol could provide an effective and well-tolerated oral treatment for CKD patients as an alternative to oral ferrous products (which are often poorly tolerated and hence ineffective) and to intravenous (IV) iron administration (which may be inconvenient and is associated with risk of allergic reaction or iron overload).

### 4.5.1 Study Population

Adult subjects will be enrolled who have a diagnosis of CKD with an eGFR of <60 and at least 15mL/min/1.73m$^2$. It is anticipated that this population will in general have less significant renal disease and comorbidities and be better able to tolerate the placebo phase of the study. Subjects will also have IDA as defined by Hb, ferritin and TSAT levels. Subjects should not be severely anemic and so will have Hb ≥8.0 g/dL. Subjects who have recently received IV iron, a blood transfusion or renal transplant will not be permitted to enter the study.

All subjects entering this study will be anemic (Hb <11.0 g/dL) which falls below the lower limit of normal Hb (13.5g /dL for males, 12.0 g /dL for females per KDOQI 2006) for investigational purposes since the benefits to subjects being treated with ferric maltol with a Hb between 11 g/dL and the lower limit of normal could be marginal. Additionally, the cut-off of 11.0 g/dL is in line with KDOQI 2006 who specify a target Hb level of 11g/dL or greater.

The inclusion criteria of <250 ng/mL ferritin with a <25% TSAT and or a <500ng/mL ferritin with a <15% TSAT is indicative of iron deficiency and representative of the population likely to benefit from iron treatment.

Subjects who develop Hb concentration decreases of ≥0.5g/dL from baseline that falls below 8.0g/dL

on 2 consecutive weeks will be withdrawn from the study and corrective measures implemented outside of the study. Withdrawal from the study would also be possible based on any AE, including anemia related symptoms, which the Investigator deemed significant. There is little data available on long or medium term Hb changes in CKD placebo treated subjects, so it is not possible to accurately predict how many subjects may have to withdraw during the 16 week placebo controlled period. However a study looking at ESA treatment in over 2000 anemic, CKD diabetic patients followed for 2.3 years showed that 55% of patients on placebo and without ESA treatment maintained a Hb >9.0 g/dL and that on average, Hb levels were either stable or increased in both the active and placebo groups (Skali 2013). The Hb decline in this study is not reported separately for hemodialysis and non-dialysis subjects, nor by iron replete or deficient subjects, however over a 2 year period the Hb decline did appear slow for most patients.

#### 4.5.2 Study Treatment Duration

Maximum treatment duration in this study is 52 weeks. Primary efficacy and safety of ferric maltol will be evaluated after the first 16 week double-blind phase after which time all ongoing subjects will receive open-label ferric maltol for up to an additional 36 weeks. Long-term safety and efficacy of ferric maltol will be examined during the open-label portion of the study. As there is a physiologically-determined limit on the amount of iron that can be absorbed from oral iron medication, the study has a 16 week placebo controlled period. This has been selected as the maximum duration likely to be clinically acceptable to achieve a meaningful Hb rise in IDA CKD patients.

This study treatment duration will continue until the last randomized subject completes the study at Week 52 or prematurely withdraws from the study.

### 4.6 RISK-BENEFIT EVALUATION

KIDGO recommends initiating treatment for IDA with oral ferrous products which are associated with GI side effects. If unsuccessful IV iron administration should be considered (see section 5.2).

This is in accordance with the labelled warnings of marketed oral iron products. The Summary of Product Characteristics (SPCs) for the various OFPs which warn that oral iron salts may have a corrosive effect that may exacerbate the symptoms associated with certain GI disease states such as peptic ulcer disease or IBD (e.g., UC). But despite this warning there are limited comparative data from prospective clinical trials investigating the AE profile of marketed oral iron products as compared to placebo or active comparators or comparing IBD to different patient populations.

The dose chosen for the Phase 3 development program, 30 mg bid, has been shown to be effective and well-tolerated in IDA patients with IBD for up to 64 weeks of treatment. In contrast to other marketed iron products, in particular ferrous drugs, the sugar derivative maltol strongly chelates iron, stabilizes iron in the less toxic ferric (Fe3+) form and renders it readily available for absorption in the intestinal tract. Consequently, the frequency of typical adverse effects is hypothesized to be reduced with administration of ferric maltol. This hypothesis is confirmed by ferric maltol being well-tolerated in patients who are intolerant to oral ferrous products in clinical studies ST10-01-301 and ST10-01-302; furthermore, unlike oral ferrous products, ferric maltol did not increase flare of underlying disease in these patients compared to placebo treatment.

The current study design does not pose additional risk for the subjects as no additional interventional procedures are planned during the study period, except for blood sampling similar to clinical routine. The patients randomized to placebo will be monitored and withdrawn should the

Hb fall ≥0.5g/dL from baseline that falls below 8.0g/dL on 2 consecutive weeks.

The intervals of Hb measurement within the schedule of study visits fall within KDOQI guidelines on monitoring Hb in patients receiving iron replacement. All patients who complete the randomized phase and remain on-treatment will enter an extended open-label phase of ferric maltol treatment and potentially benefit from iron replacement. The safety profile of ferric maltol as established from completed studies is considered acceptable and therefore the overall benefit/risk to subjects entering this study is also acceptable.

Refer to the Investigator's Brochure for further details on risk/benefit assessment.

# 5 STUDY OBJECTIVES AND ENDPOINTS

## 5.1 PRIMARY OBJECTIVE

To evaluate the efficacy of oral ferric maltol compared with placebo in the treatment of IDA in subjects with CKD at 16 weeks.

## 5.2 SECONDARY OBJECTIVE

To evaluate the efficacy, safety, tolerability and pharmacokinetics of ferric maltol in subject with IDA and CKD over a treatment duration of up to 52 weeks.

## 5.3 PRIMARY ENDPOINT

Change in Hb concentration from baseline to Week 16.

## 5.4 SECONDARY ENDPOINTS

- Proportion of subjects that achieve an increase in Hb concentration of ≥1 g/dL at Week 16.
- Proportion of subjects that achieve a Hb concentration of ≥11 g/dL at week 16.
- Change in Hb concentration from baseline to Week 8.
- Proportion of subjects that achieve an increase in Hb concentration of ≥2 g/dL at Week 16.
- Change in Hb concentration from baseline to Week 4.
- Changes in iron parameters (ferritin, TSAT, serum iron).
- AEs/SAEs

Additional long-term endpoints up to Week 52/End of Study visit similar to the efficacy and safety endpoints described above.

## 5.5 PHARMACOKINETIC ENDPOINTS

Population based PK analysis of maltol, maltol glucuronide and serum iron.

## 5.6 EXPLORATORY ENDPOINTS

Proportion of subjects with a baseline Hb of <10 g/dL that achieve a Hb > 10g/dL

# 6 INVESTIGATIONAL PLAN

## 6.1 STUDY OVERVIEW

This is a phase 3, randomized, double-blind, placebo-controlled, prospective, multicenter study. Approximately 168 eligible subjects will be randomized at a ratio of 2:1, ferric maltol to placebo.

The study will comprise of the following:

- Screening: Up to 14 days
- Randomized, Double-Blind Treatment: 16 weeks treatment with oral ferric maltol, 30 mg capsule twice daily (bid) or oral matching placebo bid.
- Open-label Treatment: Up to 36 weeks treatment with ferric maltol.
- End of Study: Week 52 or premature discontinuation.
- Post-treatment safety follow-up: 14 days following discontinuation of study medication.

Refer to Section 10 for a schematic of the study design and for details of visits and assessments.

## 6.2 INVESTIGATIONAL SITES

Approximately 35 sites will participate.

## 6.3 INCLUSION AND EXCLUSION CRITERIA

No deviations to the inclusion or exclusion criteria are permitted.

### 6.3.1 Inclusion Criteria

All of the following criteria must be met to randomize a subject in the study:

1. Ability to understand the information given in the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approved information sheet and consent form. Must sign and date the informed consent and authorization to use protected health information (PHI) in accordance with national and local subject privacy regulations prior to any study mandated procedure.
2. Willing and able to comply with study requirements.
3. Age ≥ 18 years at the time of informed consent.
4. A current diagnosis of CKD with an estimated glomerular filtration rate (eGFR) of <60 mL/min/1.73m$^2$ and ≥15 mL/min/1.73m$^2$, as calculated using the abbreviated version of the Modified Diet in Renal Disease equation (MDRD) assessed via screening laboratory results.
5. Iron deficiency anemia defined by the following criteria assessed via screening laboratory results:
    a. Hb <11.0g/dL and ≥8.0g/dL
    b. AND ferritin <250ng/mL with a Transferrin saturation (TSAT) <25% OR ferritin <500ng/mL with a TSAT of <15%
6. Female subjects of childbearing potential (including perimenopausal females who have had a menstrual period within 1 year prior to screening) must agree to use a reliable method of contraception until study completion and for at least 4 weeks following their final study visit. Reliable contraception is defined as a method which results in a low failure rate, i.e., less than

1% per year when used consistently and correctly, such as implants, injectables, some intrauterine contraceptive devices (IUDs), complete sexual abstinence, a vasectomized partner and oral contraceptive medications. Female subjects who are surgically sterile (bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or postmenopausal (defined as no menstrual period within 1 year of screening) are also allowed to participate.

### 6.3.2 Exclusion criteria

A subject who meets any of the following criteria is not eligible for participation in the study.

1. Anemia due to any cause other than iron deficiency, including, but not limited to:
    a. Untreated or untreatable severe malabsorption syndrome.
    b. Myelosuppression use (permitted if taken at a stable dose and frequency for at least 12 weeks prior to randomization and are expected to stay stable throughout the double-blind treatment period so long as there is no clinical evidence of the myelosuppression contributing to the subject's anemia).
2. Administration with any of the following prior to randomization:
    a. IV iron injection within the previous 4 weeks or administration of intramuscular or depot iron preparation within the previous 12 weeks.
    b. Single agent oral iron supplementation, taken specifically to treat anemia (e.g. ferrous sulfate, fumarate and gluconate) within the previous 2 weeks. Multivitamins are permitted.
    c. Use if ferric citrate and sucroferric oxyhydroxide within the previous 1 week.
    d. ESAs within the previous 4 weeks
    e. Blood transfusion or donation within the previous 12 weeks.
    f. Dimercaprol or cloramphenicol within the previous 7 days.
    g. Current use of methyldopa.
3. Currently receiving dialysis or initiation of dialysis is considered likely during the study.
4. Renal transplant within 12 months prior to randomization or is considered likely during the study.
5. Known hypersensitivity or allergy to the active substance or excipients of ferric maltol or placebo capsules.
6. Contraindication for treatment with iron preparations, e.g. hemochromatosis, chronic hemolytic disease, sideroblastic anemia, thalassemia, or lead intoxication induced anemia.
7. Impaired liver function as indicated by alanine aminotransferase (ALT) or aspartate transaminase (AST) > 3 times the upper limit of normal as assessed via screening laboratory results.
8. Clinically significant vitamin B12 or folic acid deficiency as determined by the screening laboratory results (retest following at least 2 weeks of starting treatment with vitamin B12 or folate replacement is permitted).

9. Pregnant or breast feeding.
10. Concomitant medical conditions with significant active bleeding likely to initiate or prolong anemia; for example coagulation disorders or recurrent GI bleeding.
11. Scheduled or expected major surgery during the course of the study. (Minor surgeries not associated with significant blood loss, in the Investigator's judgement, are permitted e.g. surgery related to fistulae or vascular access, minor dental extractions, incision and drainage of abscess or simple excisions).
12. Participation in any other interventional clinical study within 30 days prior to screening.
13. Cardiovascular, liver, renal, hematologic, psychiatric, neurologic, gastrointestinal, immunologic, endocrine, metabolic, or central nervous system disease that, in the opinion of the Investigator, may adversely affect the safety of the subject and/or efficacy of the study drug or severely limit the lifespan of the subject.
14. Any other unspecified reason that, in the opinion of the Investigator or the Sponsor make the subject unsuitable for enrolment.

### 6.4 CONCOMITANT MEDICATION

6.4.1 Not Permitted

- IV iron injections, intramuscular or depot iron administrations.
- Single agent oral iron supplementation, taken specifically to treat anemia (e.g. ferrous sulfate, fumarate and gluconate).
- Ferric citrate or sucroferric oxyhydroxide.
- ESAs.
- Blood transfusions or donations.
- Dimercaprol, chloramphenicol or methyldopa

6.4.2 Permitted

- Myelosuppressants taken at a stable dose and frequency (so long as there is no clinical evidence of the myelosuppressant contributing to the subject's anemia).
- Multivitamins containing iron.

6.4.3 Potential Medication Interactions

As some iron based medications are known to bind to other oral medications and affect absorption, ferric maltol must be administered at least 2 hours before any of these concomitant medications are taken: penicillamine, bisphosphonates, ciprofloxacin, entacapone, levodopa, levofloxacin, levothyroxine (thyroxine), moxifloxacin, mycophenolate, norfloxacin and ofloxacin.

Absorption of both iron and antibiotic may be reduced if oral iron is given with tetracycline. Administration of iron preparations and tetracyclines should be separated by 2 to 3 hours.

Absorption of oral iron may be reduced by calcium and magnesium salts (such as magnesium trisilicate). Administration of iron preparations with such compounds should be separated by at least 2 hours.

### 6.5 INDIVIDUAL WITHDRAWAL CRITERIA

Subjects have the right to withdraw consent without prejudice at any time during the study. If a subject withdraws consent, the Investigator should make a reasonable effort to determine the cause. All withdrawn subjects should have an End of Study Visit and a follow-up call 14 days after the last dose of study drug (if the subject agrees in the case of withdrawn consent).

Subjects who discontinue study treatment prior to Week 16 will be encouraged to continue with study visits and assessments up to and including assessments at week 16.

Subjects may be discontinued prematurely during the study for the following reasons:

- Withdrawal of informed consent.
- Unwillingness or inability to comply with protocol requirements.
- Pregnancy or not using a reliable method of birth control if female of childbearing potential.
- A ≥0.5g/dL decrease from baseline in Hb that falls below 8.0g/dL on 2 consecutive weeks.
- Ferritin >700ng/mL with a TSAT of >50% sustained for 2 consecutive weeks.
- SAEs that are judged by the Investigator to be related to study drug.
- Use of prohibited concomitant medications.
- Initiation of dialysis.
- Blood transfusions or donations for any cause.
- Any dose or frequency changes to myelosuppressants and/or ESAs (greater than 20% over an 8 week period) during the double-blind treatment period.
- Requirement for major surgery. Minor surgeries not associated with significant blood loss, in the Investigator's judgement, are permitted (e.g. surgery related to fistulae or vascular access, minor dental extractions, incision and drainage of abscess or simple excisions).

The reason for study drug discontinuation and the date of last dose should be recorded in the CRF.

## 7 TREATMENT OF SUBJECTS

Shield TX (UK) Limited will provide ferric maltol and matching placebo to all study sites. Sites must arrange storage of Investigational Medicinal Product (IMP) in a temperature monitored, secure location which is accessible to authorized individuals only.

### 7.1 INVESTIGATIONAL MEDICINAL PRODUCT (IMP) PRESENTATION

Ferric maltol is presented as a hard, gelatin, red capsule, 19 mm long x 7 mm diameter (size 1). Each capsule contains 30 mg iron and the following excipient(s) with known effect: 91.5 mg of lactose, 0.5 mg of Allura Red AC (E129) and 0.3 mg Sunset Yellow FCF (E110). A full list of excipients can be found in the Investigator's Brochure.

Placebo will be provided identical in appearance to ferric maltol hard, gelatin, red capsules and the same excipients with the active substance replaced with the primary excipient lactose.

### 7.2 PACKAGING

The product will be supplied in a white polypropylene securitainer with a tamper evident standard securitainer cap of white medium density polyethylene. An appropriate number of bottles containing 56 capsules will be provided to cover intervals between study visits.

### 7.3 STORAGE

IMP must be stored below 25 °C (77 °F) and must not be refrigerated or frozen. In the event that the drug is exposed to temperatures greater than or equal to 25°C, the Sponsor should be contacted for review and further instruction.

### 7.4 LABELLING

All kits and bottles will be identified by a unique kit number for the double-blind treatment period. Kits and bottles for the open-label treatment period will be clearly labelled as ferric maltol.

Labels of the IMP will contain information according to 21CFR Section 312.6.

### 7.5 DISPENSATION

Specific containers will be allocated to specific subjects via the central IXRS/randomization system for dispensation according to the treatment randomly allocated during the 16 week double-blind treatment period.

### 7.6 ADMINISTRATION

Eligible subjects will be randomized to receive one of the following treatments for the first 16 weeks of the study:

- Oral ferric maltol, 30 mg capsule bid.
- Oral matching placebo capsule bid.

Following 16 weeks of randomized treatment, all subjects will receive open-label treatment with ferric maltol for up to an additional 36 weeks.

Subjects should be instructed to take one capsule of ferric maltol (or placebo) twice daily, morning and evening, on an empty stomach (with half a glass of water), as the absorption of iron is reduced when taken with food.

If a subject forgets to take a dose he/she should take the next dose as normal. Do not take a double dose to make up for a forgotten capsule.

### 7.7 TREATMENT COMPLIANCE

Subjects will be instructed to take the study drug as described in detail on the drug labels and by the study site. Subjects will be instructed to return all unused supplies and all clinical study medication packaging at each visit. The delivery of medication to the site, its use and return, as well as subject-specific compliance, will be reconciled and documented using a Drug Accountability Form in order to monitor compliance with the medication schedule. All opened containers, together with remaining contents, and unopened containers will be kept by the Investigator in a secure, locked area until return to the drug supplier by the monitor or destruction by the site if agreed with the Sponsor. The Investigator will use the IMP only within the framework of this clinical study and in accordance with the existing study protocol.

If a subject is found to be persistently non-compliant with the study medication (defined as less than 80% or more than 120% compliant with the dosage schedule as measured at two separate visits), a decision will be made by the Investigator and Sponsor as to whether the subject should be withdrawn from the study treatment.

### 7.8 CONTINUATION OF TREATMENT

No further provisions are made for access to the study treatment under this protocol following the Week 52 / End of Study visit.

# 8 ENROLMENT AND RANDOMIZATION PROCEDURES

Full details of procedures will be provided in the Investigator Site File.

## 8.1 SCREENING

Subjects will be evaluated according to the inclusion and exclusion criteria (sections 6.3.1 and 6.3.2). Subjects will be deemed eligible for randomization if all inclusion criteria and no exclusion criteria are met. The Investigator is required to document all screened candidates considered for inclusion in this study. If excluded prior to randomization, the reasons for exclusion will be documented in the subject's medical notes and on the study screening log.

A subject may be retested once for laboratory criteria that do not meet protocol criteria so long as randomization occurs no more than 14 days from the initial test result (if eligible).

## 8.2 RANDOMIZATION

A final eligibility evaluation must be conducted immediately prior to randomization. If a subject is deemed eligible a centralized IXRS/randomization system will be used to assign the subject to ferric maltol or placebo.

Subjects will be randomized in a 2:1 ratio (ferric maltol:placebo) and will be stratified according to the subjects baseline Hb (<9.5 or ≥9.5g/dL) and eGFR (≤30 or >30mL/min/1.73m$^2$).

## 8.3 BLINDING PROCEDURES

The Investigator and site staff, subjects, monitors, Sponsor and CRO staff will remain blinded to the treatment assignment during the conduct of the randomized phase of the study. The randomization codes will be released to the Sponsor for the purpose of the primary analysis only when the clinical database for the randomized phase of the study has been locked and a final Statistical Analysis Plan (SAP) is in place.

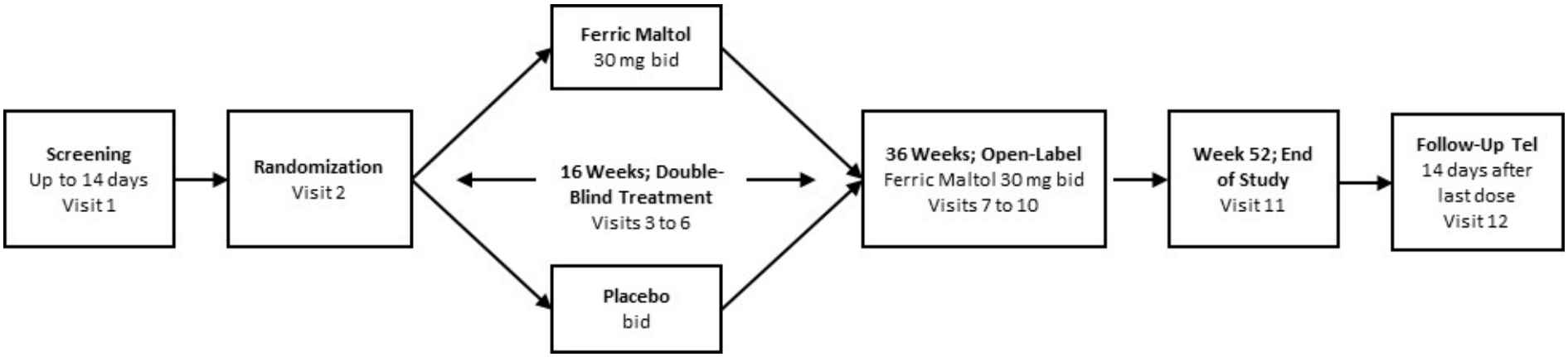
The randomization list is kept strictly confidential. It is accessible only to authorized persons who are not involved in the conduct and analysis of the study until time of un-blinding. The IXRS system will allow un-blinding by the vendor used by the Sponsor for reporting of suspected unexpected serious adverse reactions (SUSAR) as required by the regulatory agencies. The evaluation and decision as to whether a Serious Adverse Event (SAE) qualifies as an SUSAR is the responsibility of the Sponsor.

## 8.4 EMERGENCY UNBLINDING

Under normal circumstances, the blind should not be broken. The blind should be broken only if specific emergency treatment would be dictated by knowing the treatment status of the subject. It is highly unlikely that this situation will occur during this study. In such cases the Investigator can break the blind via the IXRS/randomization system. The system will encourage the Investigator to discuss the situation with Sponsor prior to breaking the code. Un-blinding will result in discontinuation of the subject from the study treatment and withdrawal from the study.

# 9 STUDY PROCEDURES

## 9.1 DESIGN SCHEMATIC



## 9.2 SCHEDULE OF ASSESSMENTS

| PERIODS | SCREENING | RANDOMIZED TREATMENT | | | | | OPEN-LABEL TREATMENT | | | | | FOLLOW-UP |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Visit Duration** | *1-14 days* | *16 weeks* | | | | | *36 weeks* | | | | | *14 days after last dose*[3] |
| **Visit Number** | *1* | *2* | *3* | *4* | *5* | *6* | *7* | *8* | *9* | *10* | *11* | *12* |
| **Visit Name** | Screening Period[1] | Randomization | Week 4 | Week 8 | Week 12 (Telephone) | Week 16 End of Randomized Treatment Period | Week 20 (Telephone) | Week 24 | Week 32 | Week 42 | Week 52 End of Study[2] | Telephone Follow-up |
| **Visit Window** | | *14 days from Screening*[1] | *±3 days of Randomization* | | | | *±7 days of Randomization* | | | | | *14-21 days after last dose of study drug* |
| **Informed Consent** | X | | | | | | | | | | | |
| **Demographics** | X | | | | | | | | | | | |
| **Medical History** | X | | | | | | | | | | | |
| **Concomitant Medications and Procedures** | X | X[4] | X | X | X | X | X | X | X | X | X | X |
| **Physical Examination** | | X | | | | X | | | | | X | |
| **Vital Signs** | | X[4] | | | | X | | | | | X | |
| **12-Lead ECG** | | X[4] | | | | | | | | | X | |
| **Urine Pregnancy Test** | X | X[4] | X | X | | X | | X | X | X | X | |
| **Hematology, Chemistry and Iron markers** | X | X[4] | X | X | | X | | X | X | X | X | |
| **Population PK Sampling**[5] | | X[4] | X | | | X | | | | | X[5] | |
| **eGFR** | X | | | | | X | | | | | X[5] | |
| **Retention Samples**[5] | | X[4] | | | | X | | | | | X | |
| **Eligibility Confirmation and Randomization** | | X[4] | | | | | | | | | | |
| **Dispense Study Drug** | | X | X | X | | X | | X | X | X | | |
| **Return Study Drug** | | | X | X | | X | | X | X | X | X | |
| **Adverse Events** | | X | X | X | X | X | X | X | X | X | X | X |

*Note: unscheduled visits may be required (e.g. repeat laboratory sampling or safety assessments).*

1. *A subject may be retested once for laboratory criteria that do not meet protocol criteria so long as randomization occurs no more than 14 days from the initial test result (if eligible).*

   *Subjects who withdraw from the study before Week 16 should have assessments conducted per Week 16/ End of Randomized Treatment Period or per Week 52/End of Study if withdrawn after Week 16.* Subjects who discontinue from study treatment prior to Week 16 will be encouraged to continue with study visits and assessments up to and including assessments at week 16.

2. *Follow-up call not required if the subject prematurely discontinued treatment and the End of Study Visit occurred 14 days after the last dose taken.*
3. *Laboratory sampling and assessments must be completed prior to the first dose of study treatment.*
4. *Population PK samples are only required at Week 52 / End of Study visit if the subject has discontinued treatment prior to Week 16. Retention samples only applicable for sites with access to a -70/80$^{O}$C freezer for storage.*

### 9.3 DEMOGRAPHICS AND MEDICAL HISTORY

The following will be documented at screening and updated (if required) prior to randomization: year of birth, race and ethnicity, gender, all current medical conditions, all medical history relevant to IDA and or CKD regardless of onset and all known iron replacement therapies. Additionally, clinically significant medical history from the past 5 years will be documented including malignancies sterilisations, hospitalizations, surgeries, ESA treatment history and the method of contraception for female subjects of childbearing potential.

### 9.4 PHYSICAL EXAMINATION

A brief physical exam will be conducted and will include body weight, height (screening only) and an assessment of general appearance, skin, head, eyes, ears, nose and throat, cardiovascular, respiratory, abdominal, gastrointestinal and musculoskeletal. The Investigator will record any clinically significant finding as an AE.

### 9.5 CONCOMITANT MEDICATIONS AND PROCEDURES

The following will be documented at screening and updated (if required) prior to randomization: all current medications at the time of screening or stopped within 12 weeks of screening and any medical procedure performed within 4 weeks prior to screening.

The following will be documented throughout the study: any medications initiated, stopped or with dose and/or frequency changes throughout the study. Any medical procedure performed throughout the study.

Medical procedures to be documented will include any therapeutic intervention such as surgery/biopsy, physical therapy or diagnostic assessment (e.g. blood gas measurement).

### 9.6 VITAL SIGNS

Blood pressure and heart rate will be measured after the subject has been supine for 5 minutes.

### 9.7 12-LEAD ECG

A 12-lead ECG will be conducted after the subject has been supine for 5 minutes.

### 9.8 LABORATORY ASSESSMENTS

All analyses will be conducted via the central laboratory unless specified. Planned assessments are for both efficacy and safety purposes. The primary endpoint of the study, hemoglobin, will be analysed via the hematology panel and will be reported in g/dL.

Investigators will review, sign and date all lab results upon receipt from the central laboratory. If a value is flagged as outside of the normal range, the Investigator must document the abnormality as ‘clinically significant’ (CS) or ‘non-clinically significant’ (NCS).

The signed paper copy of the laboratory report is retained at the investigational site. The electronic file transferred from the central laboratory to the Sponsor will be considered source data for laboratory analysis.

Full details of the required sample collection and processing procedures will be described in the Central Laboratory Manual for the study.

### 9.8.1 Hematology

Hemoglobin, hematocrit, red blood cell count, red blood cell Hb, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin (MCHC), white blood cell count (total and differential), absolute reticulocyte count, mean reticulocyte hemoglobin content (CHr), mean cell volume (MCV) and platelet count.

### 9.8.2 Chemistry

ALT, AST, alkaline phosphatase gamma-glutamyl transpeptidase (GGT), total bilirubin, creatinine, amylase, blood urea nitrogen (BUN), phosphorous, sodium, potassium, chloride, calcium, total cholesterol, uric acid, glucose, total protein, albumin. The following will be analysed during screening only: vitamin B12, C-reactive protein (CRP) and folate.

### 9.8.3 Iron Markers

Serum iron, ferritin, transferrin, total iron-binding capacity and TSAT. Soluble transferrin receptor will be analysed at baseline, week 4, week 16 and week 52 only.

### 9.8.4 Estimated Glomerular Filtration Rate (eGFR)

Analysed at screening, week 16 and week 52/End of Study only via the central laboratory using the Modified Diet in Renal Disease equation (MDRD).

### 9.8.5 Population Pharmacokinetics (PK)

Population based PK analysis of maltol and key metabolites (maltol glucuronide) will be conducted. Serum iron will also be analysed using the results collected via iron marker samples (Section 10.8.3). Single point sampling at specified visits will be conducted in accordance with FDA Guidance on Population Pharmacokinetics (February 1999). Subjects will be instructed to hold the morning dose of study drug until after the study visit. The date and time (hour and minute) of the last dose of study drug, prior to sampling, is to be recorded by the subject.

### 9.8.6 Retention Samples

Serum and plasma samples will be collected for future analysis by sites with access to a -70/80$^{o}$C freezer only. No genetic testing will be completed on any samples obtained during the study. Samples will be stored for a maximum of 5 years following the last study sample taken. Analyses will be restricted to safety related analyses and exploratory efficacy related analyses of ferric maltol related to the treatment of IDA.

### 9.8.7 Urine Pregnancy Test

Females of childbearing potential only. A urine pregnancy test should be conducted using kits provided by the central laboratory.

# 10 SAFETY

## 10.1 DEFINITIONS

### 10.1.1 ADVERSE EVENT (AE)

An AE is any untoward medical occurrence in a subject administered a pharmaceutical product and does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable or unintended sign or symptom, intercurrent illness, injury, or any concomitant impairment of the subject's health, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

A treatment-emergent AE is any AE temporally associated with the use of a study drug, whether or not considered related to the study drug.

AEs include:

- Exacerbation of a chronic or intermittent pre-existing condition/disease/symptoms present at baseline that worsen during the study including either an increase in frequency and/or intensity.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Events considered by the Investigator to be related to study-mandated procedures.
- Abnormal safety assessments, e.g. laboratory test abnormalities, physical exam findings, ECG or vital sign measurements must be reported as AEs if they represent a clinically significant finding in the medical and scientific judgment of the Investigator, symptomatic or not, which was not present at baseline or if present at baseline, worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug. However, if an abnormal laboratory or other safety-related test result is associated with clinical signs or symptoms, the signs or symptoms should be recorded as an AE. If signs and symptoms are part of a diagnosis, then the diagnosis should be recorded as AE.
- Signs, symptoms of a suspected drug interaction.
- Signs, symptoms of a suspected overdose of either the study drug or a concomitant medication (overdose per se will not be reported as AE/SAE).

AEs do not include:

- Medical or surgical procedure, e.g., surgery, appendectomy, endoscopy, tooth extraction, transfusion (as these are treatments for an AE). However, the event resulting in the procedure is an AE (e.g. appendicitis, abdominal pain).
- Pre-existing disease or medical condition documented at baseline that does not worsen.
- Situations in which an adverse change did not occur, e.g., hospitalisations for cosmetic elective surgery or for social and/or convenience reasons.
- Anticipated day-to-day fluctuations or seasonal fluctuations (e.g. allergic rhinitis) of pre-existing disease(s) or condition(s) documented at baseline.
- The disease/disorder being studied, or the expected progression, signs or symptoms (including laboratory values) of the disease/disorder being studied, unless it is more severe than expected for the subject's condition.

- Overdose of either study drug or concomitant medication without any signs or symptoms.

10.1.2 SERIOUS ADVERSE EVENT (SAE)

An SAE is any untoward medical occurrence between the time of consent and the subjects final visit that:

- is fatal,
- is life-threatening,
- requires inpatient hospitalisation or prolongation of existing hospitalisation,
- results in persistent or significant disability/incapacity,
- results in a congenital anomaly/birth defect or
- is otherwise judged as medically significant (may jeopardise the subject).

The following guidelines should be used:

Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

Inpatient hospitalisation: Subject has to stay in hospital at least overnight. The following reasons for hospitalisations are not considered AEs, and therefore not SAEs:

- Hospitalisations for cosmetic elective surgery, social and/or convenience reasons. Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalisation for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalisation for chemotherapy for cancer, elective hip replacement for arthritis, vein stripping for preventive and/or cosmetic purpose.

Prolongation of hospitalisation: Complications that occur during hospitalisation are AEs. However, if a complication prolongs hospitalisation or would have required hospitalisation or fulfils any other serious criteria, that complication is considered an SAE. In any case, admission to an intensive care unit is considered a prolongation of hospitalisation. When in doubt as to whether "prolongation of hospitalisation" was necessary, the AE should be considered serious.

Significant disability: The term significant disability means that there is a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, accidental trauma (e.g. sprained ankle) or uncomplicated chronic diseases which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

Medically significant: Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious, such as, important medical events that might not be immediately life-threatening or result in death or hospitalisation but might/may jeopardize the subject or might/may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation, or development of drug dependency or drug abuse.

SAE related to study-mandated procedures: Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as discontinuation of subject's previous treatment during a washout period, or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

## 10.2 REPORTING AND DOCUMENTATION

AEs should be documented in terms of a medical diagnosis. When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the Investigator or reported by the subject at each study visit.

Any pre-existing conditions or signs and/or symptoms present in a subject prior to the start of the study should be recorded on the Medical History CRF.

All SAEs that occur after informed consent is obtained through study completion or premature discontinuation must be documented on the AE form in the CRF and reported to the Sponsor via an SAE form within 24 hours of awareness. All AEs occurring from the time of the first dose of study treatment through study completion or premature discontinuation must be documented on the AE form in the CRF.

Any SAE that occurs during the clinical study or within two weeks of receiving the last dose of study drug, whether or not related to the study drug, must be reported to the Sponsor.

Deaths or congenital abnormalities if brought to the attention of the Investigator AT ANY TIME after cessation of study drug AND considered by the Investigator to be possibly related to study drug, should be reported to the Sponsor.

At each visit AEs will be solicited. The nature of each event should be established. Details of changes to study drug dosing or any subsequent treatment should be recorded on the appropriate pages of the CRF.

AEs already documented in the CRF (i.e., at a previous assessment) and designated as 'ongoing' should be reviewed at subsequent visits as necessary. Upon resolution, the date of resolution should be recorded in the CRF. If an AE increases in frequency or severity during a study period, a new record of the event should be started. If the AE lessens in intensity, no change in the intensity is required as only the worst intensity must be reported

All AEs and SAEs, including those that are ongoing at the end of the study or at premature discontinuation, will be followed up until resolution or stabilization or until the event is otherwise explained.

### 10.2.1 Immediate Reporting

The following AEs must be reported within 24 hours to the Sponsor or designee:

- SAEs
- Pregnancy (not considered as an AE, but must be reported immediately)

For immediate reporting, the Investigator must fill out the SAE form (also for pregnancies) and send to the Sponsor within 24 hours after awareness.

**SAFETY CONTACT DETAILS**

**Primevigilance Limited has been contracted by the Sponsor for safety reporting**

Email SAE reports to shieldpv@primevigilance.com or fax to +44 1483431831

Contact details for safety questions will be provided in the Investigator Site File

If the site obtains relevant follow-up information, this information needs to be forwarded to the Sponsor within 24 hours of awareness using a new SAE form and the updated AE form if appropriate.

Other documents must be submitted upon request. All documents must be blinded with respect to the subject's personal identification to meet data protection requirements, e.g., on the discharge summary this data must be blinded and the subject number added.

As soon as the Sponsor is informed about an SAE, an evaluation and potential reporting to central IRBs/ECs, competent authorities and other concerned parties will occur as required. The Investigator will be responsible for reporting to any local IRB/EC as required.

10.2.2 Non-Immediate Reporting

AEs that do not qualify for immediate reporting will be documented in the CRF and reported in the Clinical Study Report (CSR).

### 10.3 EVALUATION

AEs and the corresponding entries in the CRF will be reviewed by the Investigator or qualified member of the study staff.

10.3.1 Intensity

The intensity will be rated by the Investigator as "mild", "moderate" or "severe":

Mild: Symptoms barely noticeable to the subject or does not make the subject uncomfortable; does not influence performance or functioning.

Moderate: Symptoms of a sufficient severity to make the subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study.

Severe: Symptoms cause significant discomfort; incapacitation or significant impact on the subject's daily life; may cause cessation of study treatment.

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not meet the definition of seriousness. Fever of 39 °C that is not considered severe may become serious if it prolongs hospitalisation.

### 10.3.2 Causality

The following should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Not related: There is not a possibility that the event has been caused by the product under investigation. Consideration should be given to factors, including but not limited to, a lack of reasonable temporal relationship between administration of the drug and the event, the presence of a biologically implausible relationship between the product and the AE (e.g. the event occurred before administration of drug), or the presence of a more likely alternative explanation for the AE.

Related: There is a possibility that the event may have been caused by the product under investigation. Consideration should be given to factors, including but not limited to a positive re-challenge, a reasonable temporal sequence between administration of the drug and the event, a known response pattern of the suspected drug, improvement following discontinuation or dose reduction, a biologically plausible relationship between the drug and the AE or a lack of an alternative explanation for the AE.

### 10.3.3 Outcome

The outcome of each AE has to be assessed as follows:

- Fatal: The AE resulted in death ("Death" is recorded as an outcome, not as the AE)
- Ongoing/Not resolved: The AE has not resolved
- Recovered with sequelae: Resolution of the AE has occurred, but the subject retains some sequelae
- Recovered: The AE fully resolved with no observable residual effects
- Unknown: The outcome of the AE is not known as the subject did not return for follow-up and attempts to locate the subject and/or to obtain follow-up information were unsuccessful (lost to follow-up).

## 10.4 RE-EXPOSURE

If an AE requires discontinuation of IMP and is judged to be treatment-related by the Investigator or by the Sponsor, re-exposure is not allowed. If an AE requires dose reduction or discontinuation of IMP and is judged by the Investigator or by the Sponsor to be unrelated to investigational products, the decision to re-introduce the medication or to increase the dose of the medication requires prior approval of the Sponsor or designee.

## 10.5 SAFETY ENDPOINTS

During the study, safety endpoints will include treatment-emergent AEs and SAEs including clinically significant changes from baseline in vital signs, body weight, laboratory or ECG abnormalities.

# 11 STATISTICAL CONSIDERATIONS

## 11.1 SAMPLE SIZE AND POWER CALCULATIONS

A sample size of 135 subjects (Randomized 2:1, ferric maltol:Placebo, 90 in ferric maltol group and 45 placebo) will have 95% power to detect a statistically significant treatment difference of 1.0g/dL between ferric maltol and placebo on the primary endpoint, using a two-sided 0.05 significance level. This calculation assumes a common standard deviation of 1.5g/dl which is based on a pooled estimate of SDs obtained from published trials (Feraheme prescribing information 2010; Quinibi 2011; Macdougall 2014 Schwenk 2010; Singh 2006; Wyck 2005). Assuming a drop-out rate of 20%, approximately 168 subjects total will be recruited. Subjects randomization will be stratified based on baseline Hb value and eGFR.

## 11.2 STATISTICAL METHODS

### 11.2.1 Primary Endpoint Analysis

Effectiveness will be analysed by determining whether the Test group shows a statistically significant superiority as compared to the Control group.

An Analysis of Covariance (ANCOVA) will be used to analyse the primary endpoint: change in Hb concentration from baseline to Week 16. Missing change from baseline hemoglobin concentration data for week 16 will be imputed using multiple imputation methodology. This will generate 10 complete datasets containing imputed values for those missing in the original dataset. Hb concentrations at baseline, Week 4, Week 8 and gender will be considered as variables helpful in guiding this imputation. For each imputed dataset, the change from baseline to Week 16 complete datasets will be analysed using ANCOVA with factors for treatment and disease and a covariate of baseline hemoglobin and eGFR. By combining the results from these analyses, the treatment estimates will be constructed using the parameter estimates and associated standard errors. Similarly the difference of the adjusted treatment means (ferric maltol – placebo) will be presented with the associated standard error and 2-sided 95 % confidence interval.

The primary endpoint analysis will be performed using the intention-to-treat (ITT) population.

### 11.2.2 Secondary and Exploratory Analyses

Details regarding methods for analysis of secondary endpoints will be provided in the Statistical Analysis Plan (SAP). The SAP will also detail the analysis of exploratory and long-term endpoints.

No formal multiple comparisons procedure will be used to control the type I error rate for the analysis of secondary or other exploratory endpoints, including those defined for the long-term open-label phase of the study. For these analyses, confidence intervals and/or p-values will be displayed for descriptive purposes only.

### 11.2.3 Sensitivity Analyses

For the primary endpoint, the following sensitivity analyses will be performed:

- The primary analysis defined in Section 12.2.1 (with multiple imputation) will be repeated using the per protocol (PP) population.
- The ANCOVA will be repeated for the ITT population but based on observed data only (complete case analysis without imputation).

- The ANCOVA will be repeated for the ITT population but using last observation carried forward (LOCF without imputation)
- A mixed model for repeated measures (MMRM) ANCOVA will be conducted using observed data only.

Other sensitivity analyses will be documented in the SAP.

11.2.4 Imputation of Missing Data

Missing values for efficacy variables will be replaced for the secondary endpoint analyses as follows:

- For the endpoint 'Increase in Hb concentration of ≥1 g/dL at Week 16', subjects not returning to a follow-up visit will be assumed not to have reached the desired concentration.
- For the endpoint 'Hb concentration ≥11 g/dL at week 16', subjects not returning to a follow-up visit will be assumed not to have reached the desired concentration.
- For the endpoint 'Increase in Hb concentration of ≥2 g/dL at Week 16', subjects not returning to a follow-up visit will be assumed to have not reached the desired concentration.

Safety data will be used according to availability, with no imputation for missing data.

Imputation of missing values for long-term and exploratory efficacy analyses will be defined in the SAP.

11.2.5 Safety Analyses

*11.2.5.1 Adverse Events (AEs)*

AEs will be categorized by primary system organ class and MedDRA preferred term as coded using the MedDRA dictionary. The number, intensity, relation to study medication and action taken will be described by incidence tables. SAEs will be discussed separately.

## 11.3 DEFINITION OF POPULATIONS

11.3.1 Randomized Population

All subjects who are randomized.

11.3.2 Safety Population

All subjects who have had at least one dose of study drug and one subsequent contact with the Investigator will be analysed for safety.

11.3.3 Intention- To-Treat (ITT) Population (Full Analysis Set)

For efficacy, all subjects who have been randomized will be included in the ITT analysis.

11.3.4 Per Protocol (PP) Population

The PP population includes all subjects eligible for ITT evaluation and, in addition, who do not have major protocol deviations. Protocol deviations occurring during the first 16 weeks of the study will be classified as major or minor prior to study un-blinding.

## 12 ETHICAL CONSIDERATIONS

The Sponsor and Investigator must comply with this protocol, all applicable national and local regulations including International Conference on Harmonization (ICH) and Good Clinical Practice (GCP).

### 12.1 DECLARATION OF HELSINKI

The Sponsor and the Investigator must comply with the principles set forth by the Declaration of Helsinki.

### 12.2 INSTITUTIONAL REVIEW BOARD / ETHICS COMMITTEE

The Investigator must ensure that the IRB/EC has approved the protocol, the Information Sheet and Consent Form and any other required study documents prior to starting the study. The Sponsor must approve any changes to the information sheet and consent form before submission to the IRB/EC.

Prior to activation of a site and provision of IMP, the Sponsor must receive documentation to demonstrate IRB/EC approval of the required study documents, and must have completed a comprehensive site initiation training with the Investigator and site staff.

A progress report must be submitted to the IRB/EC at least annually and more frequently if required by the IRB/EC.

On completion or termination of the study the Investigator or Sponsor must submit a closeout letter to the IRB/EC (as required). A copy of the CSR synopsis will also be sent in accordance with local laws.

### 12.3 SUBJECT INFORMATION AND INFORMED CONSENT

IRB/EC approval of the written information sheet and consent form must be obtained prior to use. The Information Sheet will provide the subject with a complete and comprehensive explanation of the study including the study rationale, the procedures, the benefits and risks, that participation is voluntary and that the subject may withdraw from the study at any time without any negative consequences. In addition, a physician will discuss this information with the subject who will be given sufficient time and opportunity to have any questions answered and to make a decision of whether to participate in the study.

Written informed consent must be obtained from the subject in accordance with local practice and regulations prior to any study assessment or test being conducted. Written consent will be obtained by signing and dating the IRB/EC approved consent form.

Each consent form must also contain an authorization for the Sponsor and Investigators to use and disclose Protected Health Information (PHI) in compliance with local law.

No study assessments or procedures should be conducted until written informed consent has been provided.

A copy of the information sheet and consent form signed and dated by the subject must be given to the subject. The signed consent form(s) will be retained with the study records. A description of the consent process must be documented in the subject's medical record.

### 12.4 SUBJECT DATA PROTECTION

Prior to any study test being conducted, including screening tests, subjects must provide authorization required by local law e.g. PHI authorization in North America). Subjects will not be identified by name (or initials) in the CRF or any study reports. Data will be used for research purposes only. Every effort will be made to keep the subject's personal medical data confidential.

The subject will not be identified by name in the CRF or any study reports and all data will be used for research purposes only.

### 12.5 SUBJECT INSURANCE

The Sponsor maintains appropriate insurance coverage for clinical trials and will follow applicable local compensation laws.

### 12.6 CONFLICT OF INTEREST

Investigators should address any potential conflicts of interest (e.g. financial interest in the Sponsor) with the subject before the subject makes a decision to participate in the study.

### 12.7 REGISTRATION OF STUDY AND DISCLOSURE OF RESULTS

The Sponsor will register the study on all required registries (e.g. clinicaltrials.gov) and will post study results regardless of outcome on a publically accessible websites in accordance with the applicable laws and regulations.

# 13 STUDY MANAGEMENT

## 13.1 SOURCE DATA

The Investigator must ensure that all source documents (i.e., medical records) and CRF pages are completed and maintained according to the study protocol, and are available at the site.

The Investigator should ensure clear records are maintained that demonstrate the integrity of the data reported to the Sponsor via the CRF. This includes all original records, certified copies of clinical findings, observations or other activities necessary for reconstruction and evaluation of the study. This includes, but is not limited to, Investigator signed/dated ECGs and laboratory reports and medical notes. Source data must not be changed without clear and documented rationale. Any changes should be confirmed with the originator. A full audit trail should always be available to identify the person making the entry and/or amendments, the original entry/result, the amendment and rationale. The Investigator must ensure that source data is always attributable, legible, contemporaneous, original and accurate.

For this study, key data reported on CRFs will be verified against source documents. The CRF will not act as source except in the instance of laboratory data which will be transferred directly to the Sponsor.

## 13.2 QUALITY ASSURANCE

During and/or after study completion, Sponsor quality assurance officers, IRB/EC or regulatory authorities may perform on-site audits. The Investigator will be expected to cooperate with any audit by providing assistance and access to all requested study-related records.

## 13.3 MONITORING

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical records. The Monitor(s) will visit the Investigator at regular intervals during the course of the study and after completion of the study if needed.

During the monitoring visits, CRFs, source records and other documentation relating to the study will be made available for review. The Investigator will ensure any discrepancies or omissions are resolved.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure protocol adherence, data quality, IMP accountability, compliance with IRB/EC/regulatory requirements and continued adequacy of the investigational site, resources and its facilities to conduct the study.

Frequency and scope of the monitoring visits will be defined in the Clinical Monitoring Plan which will also define the extent of source data verification to be conducted.

## 13.4 STUDY FUNDING

Shield TX (UK) Limited is the Sponsor and provides funding for the conduct of this study. All financial details are provided in clinical trial agreements between the institution, Investigator and Sponsor.

## 13.5 CONTRACT RESEARCH ORGANIZATION (CRO)

A CRO will be contracted to be responsible for administrative aspects of the study including, but not limited to, study set-up, site initiation, monitoring, electronic CRF provision, data management

including electronic CRF provisioning, statistics and programming and reporting. Other vendors will be contracted to cover supportive services such as a central laboratory and IXR system.

### 13.6 AMENDMENTS TO THE STUDY PROTOCOL

Any significant changes to the protocol shall be submitted to the IRB/EC and Regulatory Authorities and must be approved prior to implementation as required by local law.

However, the Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, appropriate communications and notifications to the IRB/EC and Regulatory Authorities will occur as required by local law.

Amendments to the Information Sheet and Consent Form will be made if impacted by an amendment to the study protocol which will also be submitted and approved to the IRB/EC as required by local law.

### 13.7 STUDY STOPPING RULES

The Sponsor may terminate this study at any time after informing Investigators.

### 13.8 END OF STUDY

The end of study is the date of the last subject, last visit for final collection of data.

### 13.9 RETENTION OF RECORDS

The Investigator must retain the informed consent documentation, disposition of the IMP, CRFs, medical records and other source data for at least 2 years after the last approval of a marketing application in an ICH region, until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Prior to proceeding with destruction of records, the Investigator must notify the Sponsor in writing and receive written authorization from the Sponsor to destroy study records.

The Investigator must also notify the Sponsor of any changes in the archival arrangements including, but not limited to, archival at an off-site facility or transfer of ownership if the Investigator leaves the site.

In addition, the Sponsor will retain copies / originals (as appropriate) of any study-related documents in the Trial Master File until at least 2 years after the last approval of a marketing application in an ICH region, until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

### 13.10 SECURITY AND PUBLICATIONS

This study protocol remains the Sponsor property until the final fulfilment of the contract and may only be passed on to registration authorities and license partners with the Sponsor / Applicant's approval. The study site will treat all knowledge about the study product and/or its manufacturer with strictest confidentiality.

The Sponsor ensures that substances used in the manufacture of the IMP are generally known in pharmaceutical science and have been released by the appropriate national authorities for use in medications, cosmetics or food.

Publication rights will be described in the Investigator contract. The study site's agreement is not required for using the study results for discussions with regulatory/governmental authorities or for other purposes such as presentation at conferences, discussion with potential licencing partners or specialist groups.

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