International, multicenter, observational study to assess the efficacy and safety of L-cysteine in patients on hemodialysis for Chronic Kidney Disease 5

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L-Cysteine™

- L-Cysteine oral dietary supplement
- L-Cysteine 700mg in two layer tablet characterized by different release the first layer quickly releases 350mg and the second layer releases 350mg in a longer time 6-7hrs
- L-Cysteine is aimed at enhancing the Glutathione (GSH) in the body to counteract the oxidative stress and the consequent shorter life of erythrocytes
- Cysteine is completely safe to consume just like any other natural food; recognized by the FDA as GRAS and approved by the EFSA

Study Objectives

Primary

- to assess the effectiveness of L-Cysteine on hemoglobin and hematocrit in HD patients

Secondary

- to assess the safety profile of L-Cysteine

- to assess the effect of L-Cysteine on the levels of reduced and oxidized glutathione (GSH and GSSG).

Study endpoints

- The **primary variables** for the assessment of L-cysteine effectiveness will be **hematocrit** and **hemoglobin** measurements at **baseline** and at **weeks 4, 8, 12, and 16**. The **absolute and relative difference** of hematocrit and hemoglobin between baseline and last study visit will be calculated
- The **secondary variables** i) for the assessment of the L-cysteine's safety profile is **adverse event reporting** throughout the study and 4 weeks following last study visit and ii) for the assessment of the effect of L-cysteine on glutathione, **GSH and GSSG** will be measured at baseline and weeks 4, 8, 12, and 16

Study design

- Run-in period (1 week) - Informed consent and inclusion and exclusion criteria. Hemoglobin and hematocrit need to be recorded at baseline. Kt/V, AST, ALT, Tsat, ferritin and CRP will be recorded. GSH and GSSG will be measured.
- Treatment period (16 weeks) – patients report to the nephrology center 3 times a week for their scheduled HD sessions. Hemoglobin and hematocrit, Kt/V, AST, ALT, Tsat, ferritin and CRP, GSH and GSSG will be measured at weeks 4, 8, 12, and 16. Adverse events will be recorded throughout the study and 4 weeks after last study visit

Treatment continuation with L-Cysteine after study completion remains at the investigator's discretion

Dosing Scheme

- One L-Cysteine tablet every day (at the beginning of the day). On dialysis days (3 dialysis/week), two L-Cysteine tablets will be administered; one tablet prior and one after the dialysis session. Therefore, every patient will be receiving 10 L-Cysteine tablets per week.
- To be stored in a dry environment below 25°C.

Safety profile

- No side effects have been reported. Rarely, it can cause rashes, headache, drowsiness, low blood pressure.
- Not to be given to individuals suffering of cystinuria.
- All adverse events will be recorded and reported throughout the study and 4 weeks after last study visit. Abnormal laboratory findings, which cannot be attributed to the patient's clinical condition, will be reported as adverse events.

Inclusion criteria I/II

- Adult male and female (Age range 18-79 years)
- Clinically stable patients on regular HD, three times a week for at least six months. HD duration must be stabilized between 3 h and 5 h.
- A dialysis adequacy, expressed as equilibrated Kt/V (total fractional urea clearance) $\geq$ 1.05.
- Patients who have been receiving stabilized EPO treatment for at least three months and with Hb concentration >9 g/dl and <12 g/dl at baseline
- Arteriovenous fistula or stabilized access graft

Inclusion Criteria II/II

- Stable administration (dose and frequency) of iron in the 3 months prior to study entry
- Transferrin saturation between 20% and 50%, from 3 months prior to study entry
- Serum ferritin between 100 ng/ml and 800 ng/ml, from 3 months prior to study entry
- Mean corpuscular volume between 80fL and 100fL
- Written informed consent to study participation

Exclusion criteria I/III

- Hemodialysis catheter or unstable vascular access graft
- Patients in waiting list for a kidney from an alive donor
- Patients having received blood transfusion in the 3 months prior to study entry
- Unstable clinical condition in the 3 months preceding study entry (i.e. acute infection)
- Present or past history (in the previous 2 years) of malignancy, including melanoma (other skin neoplastic lesions are accepted)
- History of stroke or MI in the previous 6 months

Exclusion Criteria II/III

- Presence of major systemic illnesses other than renal: type 1 diabetes mellitus, liver disease with AST and/or ALT 3 times higher than the upper reference limit, neurological or psychiatric disease
- Concurrent use of systemic anti-inflammatory drugs, glucocorticoids, androgen steroids, cyclo-phosphamide, cyclosporin, azathioprine
- Use of vitamin E (tocopherol), selenium, vitamin C (ascorbic acid) within three months of study entry, at a daily dosage more than three times higher than RDA (i.e. 8x3=24 mg for vitamin E, 45x3=135 µg for selenium, 60x3=180 mg for vitamin C)
- Concurrent drug treatment with ACE inhibitors and angiotensin II antagonists, if not administered at a stable dose for at least 3 months prior to study entry

Exclusion Criteria III/III

- Use of NAC (any dosage) within three months of study entry
- Known or suspected hypersensitivity to NAC
- Convective dialysis techniques in the preceding three months (hemodiafiltration, hemofiltration)
- Participation, in the 3 months preceding enrolment into the study, in any other clinical study in which investigational or marketed drugs were employed
- Pregnant or intention to become pregnant women not following highly effective contraceptive methods.
- Patients with gastrointestinal pathology and severe secondary hyperparathyroidism

Flow chart

	Baseline	Week 4	Week 8	Week 12	Week 16	Study completion
Informed consent	**X**					
Demographic data Medical history	**X**					
Inclusion-exclusion criteria	**X**					
L-Cysteine		**day1 – day 112 one tablet every day and two tablets on dialysis days**				**To be continued at investigator's discretion**
Adverse event recording		**day1 – 4 weeks after last study visit**				
Hemoglobin - hematocrit	**X**	**X**	**X**	**X**	**X**	
Glutathione	**X**	**X**	**X**	**X**	**X**	
Lab parameters	**X**	**X**	**X**	**X**	**X**	