Statistical analysis plan

A Phase II Study to Evaluate the Efficacy of imlifidase (IgG endopeptidase) to Desensitize Transplant Patients with a Positive Crossmatch Test

Sponsor:	**Hansa Medical AB, Lund, Sweden**
Contract research organisation:	[redacted]
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Investigational product name:	**Imlifidase, previously HmedIdeS / IdeS**
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Signature page

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Table of contents

List of abbreviations and definition of terms

ADA	Anti-drug antibody
ADaM	Analysis data model
AE	Adverse event
AUC	Area under the concentration versus time curve
BMI	Body mass index
BP	Blood pressure
CDC	Complement dependent cytotoxicity
C_{max}	Maximum observed concentration
CRF	Case report form
CV	Coefficient of variation
DSA	Donor specific antibodies, anti-human leukocyte antigen (HLA) donor-specific antibodies
ECG	Electrocardiogram
FACS	Fluorescence-activated cell sorting
IMP	Investigational medicinal product
LD	Living donor
LLOQ	Lower limit of quantification
MedDRA	Medical Dictionary for Regulatory Activities
NCA	Non compartmental analysis
PD	Pharmacodynamics
PK	Pharmacokinetics
PP	Per-protocol analysis set
PRA	Panel reactive antibody
PT	Preferred term
SAB-HLA	Single antigen beads - human leukocyte antigen
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Safety analysis set
SD	Standard deviation
SE	Standard error
SOC	System organ class
SDDM	Study data tabulation model
$T_{½}$	Elimination half-life
TEAE	Treatment emergent adverse event
TLF	Tables, listings and figures
T_{max}	Time of observed C_{max}

1 Introduction

This document describes the planned statistical analyses for study 15-HmedIdeS-06 which will include data processing, data analyses and data presentation. This SAP is based on the protocol version 5.0 applicable for USA dated 20 March 2017, version 6.1 applicable for Sweden dated 14 June 2017, and version 7.2 applicable for France dated 13 September 2017. The differences between the country specific protocol versions only relate to inclusion criteria and will not influence the presentation of data.

The original planned collection of data was later extended by amendment 7, dated 8 December 2017. An additional CRF was designed to include donor characterisation, recipients' previous transplantation history and transplantation outcome.

1.1 Study objectives and endpoints

1.1.1 Objectives

The primary objective of this study is:

- To assess the imlifidase efficacy in creating a negative crossmatch test

The secondary objectives of this study are:

- To determine DSA levels at multiple times (pre-dose, 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180) post imlifidase treatment
- To determine time to creating a negative CDC crossmatch test
- To determine time to creating a negative FACS crossmatch test
- To evaluate safety parameters (adverse events, clinical laboratory tests, vital signs and ECGs) following imlifidase treatment up to day 180
- To monitor kidney function after imlifidase treatment as assessed by, filtration (eGFR), creatinine and proteinuria
- To establish the PK profile of imlifidase
- To establish the PD profile of imlifidase (cleavage and recovery of IgG)
- To establish the immunogenicity profile of imlifidase (ADA)

1.1.2 Endpoints

The primary endpoint of this study is:

- Efficacy defined as imlifidase ability to create a negative crossmatch test within 24 hours

after imlifidase dosing

The secondary endpoints of this study are:

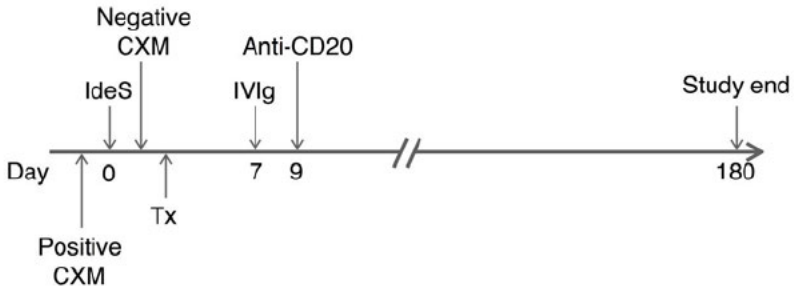
- DSA levels at pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180 post imlifidase treatment

- Time to creating a negative CDC crossmatch test
- Time to creating a negative FACS crossmatch test
- Safety parameters (adverse events, clinical laboratory tests, vital signs and ECGs)
- Kidney function after imlifidase treatment assessed by, filtration (eGFR), creatinine and proteinuria up to 180 days post treatment
- PK profile of imlifidase up to day 14
- PD profile of imlifidase (cleavage and recovery of IgG) up to day 180 post imlifidase
- Immunogenicity profile of imlifidase by measuring ADA

2 Study design

This is a phase II, open label exploratory study to assess the imlifidase efficacy in creating a negative crossmatch test (CXM) in a total of 15-20 patients (7-13 with living donors and 7-13 with a deceased donor) who exhibit DSAs and have a positive crossmatch test to their available live donors. The first 3 patients in this study will receive a kidney from a deceased donor. The study will primarily examine the efficacy of imlifidase in creating a negative CXM in patients. Included patients will be treated with imlifidase on day 0. If it is considered safe and the desired effect is not achieved (negative crossmatch) a second dose can be given within 2 days of the first infusion. In addition to imlifidase patients will be given high dose IVIg (2 g/kg BW, maximum of 140 g) on day 7 and anti CD20 (Rituximab) on day 9 as outlined in Figure 1. DSA levels will be monitored 2, 6, 24 and 48 hours and 7, 14, 21, 28, 64, 90, 120 and 180 days after the last imlifidase dosing. Safety, including kidney function will be monitored at multiple time points up to 180 days after treatment. PK, PD and ADA will be followed. For details on assessments see flow chart in Table 1. Patients who are not eligible for transplantation after imlifidase treatment will not be transplanted and thus will not receive any induction therapy or immunosuppression. All patients who receive imlifidase will also be asked to remain in the study and be followed up according to the study protocol even if they are not transplanted. In addition, patients who lose their graft during the course of the study will remain in the study and be followed up according to the study protocol and clinical practice at the respective site.

Figure 1 Study design



2.1 Overview of study procedures

Table 1 Study flow chart: Screening to day 180 after imlifidase infusion

Study visit	1	2	3	4	5	6	7	8	9	10	11	12
Day	-28-0	0-2	3-6	7	9	14	21	28	64	90	120	180
Assessment /Time window	Screening			+/-1 d	+2 d	+/- 2 d	+/- 3 d	+/- 3 d	+/-7 d	+/-7d	+/-14 d	+/-14 d
Informed Consent	X											
Demographics and medical/surgical history	X	X										
Inclusion/exclusion	X	X										
Physical examination	X											X

Weight	X	X				X						
Height	X											
Vital signs	X	X		X[c]				X		X	X	X
Body temperature	X	X										
CDC and FACS	X	X[a]										
DSAs	X	X		X[c]		X	X	X	X	X	X	X
Pregnancy test (serum)	X	X[h]										X
Sperm sample	X[k]											
Adverse events		X	X	X	X	X	X	X	X	X	X	X
ECG	X											X
Drug infusion		X										
Safety laboratory tests	X	X		X[c]		X	X	X	X	X	X	X
HIV and hepatitis	X											
P-creatinine (eGFR)		X		X[c]		X	X	X	X	X	X	X
Proteinuria						X		X	X	X	X	X
U-protein electrophoresis		X[d]	X[d]	X[d]	X[d]							
PK sampling		X	X[f]	X[c]	X[g]	X						
PD sampling (IgG)		X		X[b]	X[g]	X	X	X	X			X[L]
ImmunoCAP IgG (ADA)		X		X[b]		X	X	X	X	X	X	X
ImmunoCAP IgE	X											
Virus screen (BK-, EBV, CMV-PCR)	X					X		X	X	X		
Methylprednisolone Loratadine		X										
Rituximab					X[e]							
High dose IVIg				X[i]								
Kidney biopsy		X[j]										X
Check concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X

Day 0 is the imlifidase dosing day

[a] For LD patients the screening crossmatch test must be repeated pre-dose

[b] PD (IgG) and ADA samples will be taken pre- and postdose IVIg on day 7

[c] This assessment will be done prior to IVIg infusion

[d] 24 hour urine collections for protein electrophoresis will be performed daily until day 9

[e] Rituximab can be given day 9-11 if a longer time window is required for practical reasons

[f] PK will be drawn at 96 hours ±4h

[g] PD (IgG) and PK samples will be drawn prior to Rituximab infusion on day 9-11

[h] If a female patient has been hospitalized between screening visit and visit 2, a pregnancy test at screening visit will suffice and a pregnancy test at visit 2 is not required

[I] If deemed necessary by the investigator this dose may be split into two doses administered over days 6-8

[j] A biopsy will be performed on the donor graft prior to transplantation (for DD transplantations)

[k] Precautionary sperm sample on patient's request (applicable only for France)

[L] PD sample at visit 12 was removed on January 18, 2018 (Amendment 8)

Table 2 Study flow chart from 0 (pre-dose) to 48 h after imlifidase infusion. Time-points after dosing (0) relates to start of infusion

Study visit	2					
Day	0/ Pre-dose	Dosing	2h	6h	24h	48 h
Assessment /Time window	≤ 60 min	0	+/- 15 min	+/- 30 min	+/- 2h	+/- 2h
Demographics and medical/surgical history	X					
Inclusion/exclusion criteria	X					
Weight	X					
Vital signs (BP & pulse respiratory frequency)	X		X	X	X	X
Body temperature	X		X	X	X	X
CDC and FACS CXM	X		X	X	X	
DSAs	X		X	X	X	X
Pregnancy test (serum)	X[c]					
Adverse events	X	X	X	X	X	X
Drug infusion		X				
Safety laboratory tests	X		X	X	X	X
P-creatinin, eGFR					X	X
U-protein electrophoresis					X[b]	X[b]
PK sampling	X		X	X	X	X
PD sampling (IgG)	X		X	X	X	X
ImmunoCAP IgG (ADA)	X					X
Methylprednisolone Loratidine[a]	X					
Check concomitant medication	X		X	X	X	X

Assessments will be repeated from the pre-dose timepoint if a second dose of imlifidase is given

[a]Premedication with methylprednisolone and loratadine will be repeated before the second imlifidase dose

[b]24 hour urine collections for protein electrophoresis will be performed daily until day 9

[c]If a female patient has been hospitalized between screening visit and visit 2 a pregnancy test at screening visit will suffice and a pregnancy test at visit 2 is not required

2.2 Determination of sample size

Sample size is not based on formal statistical considerations. Due to the nature of the primary endpoint of the study it is expected that data from 15-20 patients should suffice to achieve the objectives of the study. Also, the sample size is in line with experience from previous similar phase II studies with other compounds to obtain adequate safety, tolerability and PK data to achieve the objectives of the study.

2.3 Blinding

The study is open-label.

2.4 Data pre-processing

Data sets

The export data sets from the [redacted] data management database will be transformed into SDTM structure and format following the implementation guide version 3.2 (current version) and also following "Therapeutic Area Data Standards User Guide for Kidney Transplant Version 1.0 (Provisional)". ADaM data sets will be prepared based on the SDTM data sets following implementation guide version 1.1 (current version). Tables, figures and listings will be prepared from the ADaM data sets.

Derivation of pharmacokinetic parameters

PK analysis of the serum concentration data for imlifidase will be performed at Hansa Medical. The actual sampling times will be used in the parameter calculations. Concentration-time raw data and PK parameters will be calculated for each individual as well as reported per received dose(s).

In earlier clinical studies with imlifidase an open 2-compartment model was found to best describe the data. The model can be described by model parameters V (volume of central compartment), K21, Alpha and Beta. A similar approach will be applied to this study and non-compartmental parameters can be calculated from these model parameters as secondary parameters by standard PK equations, including where possible: the area under the curve to infinite time (AUC), the terminal half-life ($T_{1/2}$), clearance (CL), volume of distribution at steady-state (V_{ss}) and volume of distribution during the elimination phase (Vz). In addition, C_{max} and T_{max} may be obtained directly from the experimental data.

3 Analysis sets

The analysis sets will be determined at the data review prior to database lock. Decisions will be documented in the database lock minutes.

3.1 Safety analysis set

The safety analysis set (SAS) will consist of all patients that received any amount of study medication.

3.2 Per protocol analysis set

The Per protocol analysis set (PP) will consist of all patients in the safety set that has recorded at least one efficacy endpoint value. Data from patients with one or more major protocol violations are excluded. The PP analysis set will be used for presentation of efficacy, pharmacokinetic, and pharmacodynamic endpoints.

4 Statistical analyses and presentation of data

4.1 General considerations

No formal statistical hypothesis testing will be performed in this study. All presentation of data will be descriptive by nature. Missing data will in general not be imputed or adjusted for in other ways.

The protocol states that tabulations will be by actual dose received. The protocol allowed for the DSMB to decide on dose escalation. All patients were administered planned dose(s) of 0.25 mg/kg BW. For one patient the actual dose was reduced due to an allergic reaction. For 3 patients the protocol option of administering a 2nd dose was used. Efficacy and safety tabulations will be by number of administrations (1 or 2 doses) and total including all patients. The patient with reduced dose [redacted] will be included in the "1 dose" group for safety evaluation but excluded from the PP.

Numerical data will be presented in summary tables by number of patients, arithmetic mean (geometric mean and coefficient of variation [CV] where applicable), median, standard deviation (SD), minimum and maximum. Categorical data will be presented by number and percent of patients as well as number of events (where applicable).

Endpoints will be presented graphically as mean profile plots, individual profile plots and spaghetti plots. The sampling frequency is for efficacy and some safety endpoints high from pre-dose until 48 hours followed by decreasing frequency. Therefore, the graphical presentation will, in most cases, be as box plots with a categorical x-axis. For other data, a plot with linear x-axis (0 to 180 days) may be supplemented with a subset plot where only the first 24 or 48 hours are included on the x-axis.

All data will be listed. Auxiliary database parameters will not be included. Listings will be sorted by patient ID, parameter and time point. In general listings will not be mentioned in detail below.

The study did not include any interim analyses.

4.2 Patient disposition

A patient disposition table will include the number of patients screened, patients in the safety, PP analysis sets, completers and withdrawals with reason for withdrawal, and finally patients by visit will be summarised with frequency and percentage.

The patients screened but not allocated to treatment will be presented with the reason(s) for screening failure in a listing

All major protocol deviations will be summarised with frequency and percentage for each category of protocol deviation.

4.3 Demographics and other baseline characteristics

The following demographic and body measurements variables will be summarised: age, sex, race, height, weight and BMI.

Medical and surgical history and concomitant illness will be summarised by MedDRA system organ class (SOC) and preferred term (PT) version 18.1. Prior and concomitant medication will be tabulated by WHO drug version 153E, level 4 (chemical/therapeutic/pharmacological subgroup) and level 5 (Chemical substance). Medication is categorised as "Started prior to study start" and "Ongoing" in the eCRF and these responses will be used to categorise as prior and concomitant respectively. Medication was recorded in the original eCRF. The additional data recording collected specifically medication for de-sensitization and rejection. There may therefore be an overlap with prior and concomitant medication and the de-sensitization and rejection medication will be tabulated separately.

Previous kidney transplant history will be summary tabulated.

Baseline assessments of ECG, physical examination, vital signs, body measurements and laboratory parameters will be presented as part of the general tables and listings for these parameters.

ImmunoCAP IgE (ADA) is recorded at baseline only and will be listed. Serology and sperm sample will be listed.

The drug exposure will be listed showing number of doses, planned dose and actual dose per kg BW.

Donor characteristics will be listed.

Recipient and donor HLA types will be listed.

Recipient and donor blood groups will be listed.

Deceased donor characteristics will be listed.

Protocol deviations will be listed.

4.4 Efficacy

4.4.1 Primary efficacy analysis

The primary efficacy endpoint is defined as imlifidase ability to create a negative crossmatch test within 24 hours after imlifidase dosing. The primary endpoint will be presented for the PP analysis sets.

The planned time points (according to the flowchart) are: Screening, pre-dose, 2h, 6h, 24h, and 48h. In general, only the pre-dose and 24h analyses are performed, while the other planned analyses are missing. For each of the crossmatch tests (FACS B-cell, FACS T-cell, amplified and non-amplified analyses of CDC B-cells and CDC T-cells, and virtual) summary tabulations by time point will be made.

For each patient an overall response is defined as positive if at least one of the assays is positive at pre-dose and all recorded assays are negative at 24h. The overall response is summary tabulated.

4.4.2 Secondary efficacy analyses

Secondary efficacy endpoints will be presented for PP.

SAB-HLA

SAB-HLA levels (MFI) are determined at pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180 days post imlifidase treatment. Positive SAB-HLA are defined as having pre-dose levels above 3,000 MFI. The SAB-HLA will be listed by patient flagging positive (yes/no) and donor specific SAB-HLAs. The positive SAB-HLA will be summarised and presented in box-plots.

DSA

DSA levels (MFI) are determined at pre-dose and 2, 6, 24 and 48 hours and days 7, 14, 21, 28, 64, 90, 120 and 180 post imlifidase treatment. The DSA will be summarised by patient and time point. DSA will be presented graphically as scatter plots (MFI versus time) with one separate plot for each patient. The x-axis in these plots will be with the nominal time points and therefore not linear in the time variable. For this reason the scatter plots will be without connecting lines.

Pharmacodynamics

The PD profile of imlifidase (cleavage and recovery of IgG) is recorded up to day 180 post imlifidase dosing. PD will be summary tabulated by time point and presented graphically as mean profile versus time and as spaghetti profile plots.

All PD data will be presented for the PP analysis set.

Time to negative crossmatch

The time to creating a negative crossmatch is specified in the protocol as an endpoint. However, due to many missing values and in particular missing data for time points between pre-dose and 24 hours, the Time to creating a negative cross match will not be calculated. Crossmatch data will be listed.

Pharmacokinetics

The PK profile of imlifidase is recorded up to day 14. The PK concentrations will be summary tabulated by time point. The PK summary tables will not include total columns. Further, the PK concentrations will be presented graphically as mean profile plots by number of doses and as spaghetti plots. Semi-log format with log10 y-axis and a linear time x-axis will be presented.

The PK parameters are derived as described above under pre-processing by compartment modelling. Further NCA parameters are calculated from the compartment parameters. Both types of PK parameters will be summary tabulated. In addition to standard summary measures, $t_{1/2}$ will be described by the harmonic mean.

Imlifidase values <LLOQ (LLOQ = 0.10 µg/mL) will be presented as 0.5*LLOQ for summary tables and figures.

All PK data will be presented for the PP analysis set.

4.4.3 Additional analyses

Calculated PRA (cPRA) values will be summarised using the undiluted categories <80%, 80.00% - 97.50%, 98% (97.51% - 98.50%), 99% (98.51% - 99.50%), > 99% (99.51% – 100%).

Additionally, the diluted and undiluted cPRA values will be plotted against the different cut-off for unacceptable HLA.

4.5 Safety

Safety parameters will be evaluated for the safety analysis data set.

4.5.1 Adverse events

Adverse events (AEs) will be classified according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

A treatment emergent adverse event (TEAE) is any AE occurring after the administration of the IMP and within the time of the residual effect period or a pre-treatment AE or pre-existing medical condition that worsens in intensity after administration of the IMP and within the time of the follow up period. Based on the half-life and the PD properties of imlifidase the residual drug effect is considered 30 days after administration.

An AE overview summary table will be prepared including the number of patients reporting an AE, the percentage of patients (%) with an AE, and the number of events (E) reported for the following categories:

- TEAEs
- Related TEAEs
- Serious TEAEs (SAEs)
- TEAEs leading to withdrawal
- Deaths

Treatment-emergent AEs will be summarised in a table by dictionary level, i.e., SOC and PT for MedDRA. The table will display the total number of patients reporting an AE, the percentage of patients (%) with an AE and the number of events (E) reported. AEs will be presented by SOC and PT sorted in decreasing frequency of occurrence.

Summary tables will be prepared for:

- All TEAEs
- TEAEs by causality (related/unrelated)
- TEAEs by intensity
- Related TEAEs by intensity
- SAEs
- SAEs by causality (related/unrelated)

Data listings will be provided for:

- All TEAEs sorted by patient number and start time
- All TEAEs sorted by MedDRA SOC and PT

- SAEs
- SAEs leading to death
- TEAEs leading to discontinuation of study drug
- TEAEs leading to withdrawal
- Pre-treatment AEs
- Post-treatment AEs

4.5.2 Other safety endpoints

Clinical laboratory tests will be summary tabulated and presented graphically as box plots.

The immunogenicity profile of imlifidase is evaluated by measuring ADA, which will be be summary tabulated and presented graphically as box plots.

Vital signs will be summary tabulated.

ECG will be listed.

The kidney function after imlifidase treatment is assessed by kidney biopsies on day 180, filtration rate (eGFR), plasma creatinine and proteinuria up to 180 days post treatment. These variables are all presented together with the safety laboratory tests. Each variable will be tabulated by time point

The eGFR will be calculated as described in the MDRD equation [1]:

eGFR (mL/min/1.73 m2) = $175 \times (sCr)^{-1.154} \times (Age)^{-0.203} \times (0.742$ if female) $\times (1.212$ if African American),

where sCr stands for creatinine value in serum.

4.6 Other endpoints

Not applicable.

5 Deviations from protocol analysis

The protocol stated that PK analysis of the serum concentration data for imlifidase would be performed at the appointed CRO on behalf of sponsor, but it will be performed by the Hansa Medical responsible pharmacokineticist.

6 Quality control

The quality control of the data will be performed as follows:

- By Hansa Medical for all lab data that Hansa Medical produce or receive and handle before forwarding to [redacted]
- By [redacted] Data Management for all data following the data validation plan
- By [redacted] Statistics and Programming for all data received as either Trial Master export or directly from Hansa Medical

Concerning the last bullet above, the QC depends on the process below, but it will follow [redacted] Single Use Programs:

SDTM data sets will be generated by programs in the Statistical analysis system (SAS) by reading in lab data and export data from Trial Master and converting to SDTM formats following the SDTM specifications. The QC will include:

- Independent Code review
- CRF annotation review vs SDTM content
- Direct QC of input vs output in SDTM on a sample of data

This three-pronged approach has proven to give a high quality level corresponding to the expected for SDTM data

ADaM data sets will be based on the SDTM data sets. The programming of the ADaM datasets will be performed in SAS and the programs will be reviewed by an independent person.

Tables, listings and figures (TLF) will be created by SAS programs and based on the ADaM data sets. Summary TLFs will be QC'ed by independent code review.

On top of the actual code review for ADaM and TLF, the review includes check of execution, error log, check for warnings and important notes, and check of output. On top of reviewing individual programs and output items, an integrated review of all output will be performed by a reviewer. Since there are no formal statistical analyses double programming will not be applied in this study.

The programming and execution of programs for producing data sets and tables, figures and listings follow the [redacted] SOPs [redacted] on standard programs, programming environment and single use programs respectively.

SAS version 9.4 or later will be used for data handling and presentation.

7 Layout of output

TLF shells are presented in a separate document. The planned table of content will also be presented separately. The final output may deviate slightly as decisions on numbering and layout of TLF and similar may be updated after signature of this SAP.

The output will follow [redacted] standard output templates. Tables and listings will first be prepared as individual RTF (Rich text format, which is a standard text format) files. This file type may be opened and saved in the currently available Microsoft Word versions. Graphical output will be prepared in PNG (Portable network graphics) format, which is the standard graphical format in current Microsoft software packages and therefore easily importable into Microsoft Word documents.

Tables and figures will per default be created in portrait format while listings will be in landscape format. Margins and font will be chosen to respect the requirements for filing with EMA (European medicines agency) and FDA (the US Food and drug administration).

The output items (tables, listings, figures) will be collected in Word documents as described in the TOC below. Separate Word documents will be created for tables (called 14.1), figures (called 14.2), and listings (called 16) respectively.

8 Tables, listings and figures

Tables and figure templates are prepared as separate documents. And overall table of content for the output is also maintained as a separate document. Templates and the table of content are working documents and may be updated also after the signature of the SAP.

9 References

1. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009; 150(9): 604-12.

10 Change log

Version	Effective date	Reason for revision
1.0	13-Jul-2018	New document