POPULATION PK ANALYSIS PLAN

Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI

Protocol number:	GDX-44-015 (V4, 9 October 2024)
Drug name:	gadopiclenol
Drug development phase:	Phase II
Sponsor:	Guerbet B.P. 57400, 95943 Roissy CdG Cedex, FRANCE
Pharmacometrician:	PPD PhinC Development 36, rue Victor Basch 91300 Massy PPD
PhinC reference:	PH21036
Version - date:	Version 2.0- 29/10/2024
Reason for amendment	The possibility to perform an analysis before the recruitment is completed was introduced with the methodology to be applied to simulate the exposure in not recruited groups (at the time of analysis). A correction was made on the covariate model section to replace eGFR by serum creatinine as requested by authorities

2 SIGNATURE PAGE

I herewith declare that I agree without reservation to the methods described in detail in this document:

Author: PPD **Pharmacometrician, Phinc Development**	Date: Signature: PPD
Approval: PPD **PK expert, Guerbet**	Date: PPD Signature:
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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

α	Type I error for test statistics
η	Random effect for Inter-individual variability, assumed to be distributed according to N (0, ω^2)
ε	Random effect for residual variability/error, assumed to be distributed according to N (0, σ^2)
σ^2	Variance for residual variability
θ	Fixed effect parameter (of structural model or covariate)
ω^2	Variance for Inter-individual variability
AP	Analysis Plan
AUC	Area Under the Curve
BLQ	Below Limit of Quantification
BMI	Body Mass Index
BW	Body Weight
CI	Confidence Interval
CL	Clearance
COV	Covariate
CV	Coefficient of Variation
CWRES	Conditional Weighted RESiduals
EBE	Empirical Bayes Estimates
eGFR	estimated Glomerular Filtration Rate
EMA	European medicinal agency
ESRD	End Stage Renal Disease
FO	First Order estimation method
FOCE	First Order Conditional Estimation method
g	gram
Gd	Gadolinium
GdCA	Gadolinium based Contrast Agent
GM	Geometric Mean
GOF	Goodness Of Fit
h	our(s)
HV	Healthy Volunteers
IIV	Inter Individual Variability
IMP	Investigational Medicinal Product
IPRED	Individual PREDiction
IQR	Inter-Quartile Range
IWRES	Individual conditional Weighted RESiduals
IWRS	Interactive Web Response System
IV	Intravenous
kg	kilogram(s)
L	Liter(s)
LLOQ	Lower Limit Of Quantification
LRT	Likelihood Ratio Test
Max	Maximum
MC	Monte Carlo simulation
Min	Minimum
min	minute(s)

mL	milliliter(s)
MDV	NONMEM Missing Dependent Variable
mol	mole
mmol	millimole
MRI	Magnetic Resonance Imaging
N	Number of observations
Nmiss	Number of missing observations
NONMEM	Nonlinear Mixed Effects Modelling Software
NPDE	Normalized Prediction Distribution Errors
OF	NONMEM Objective Function
pcVPC	prediction corrected VPC
PK	Pharmacokinetic(s)
PMA	Post-menstrual age
PopPK	Population PK
PPC	Performance Predictive Checks
PRED	concentration PREDicted by the population model
QC	Quality Control
RI	Renal Impairment
RSE	Root Square Error calculated as percent relative standard error
Screat	Serum creatinine
SD	Standard Deviation
SE	Standard Error
$t_{1/2}$	Terminal half-life
TSRB	Trial Safety Review Board
V	Volume of distribution
WRES	Weighted RESidual

5 INTRODUCTION

The purpose of the Population Pharmacokinetics (PopPK) analysis plan (AP) is to give details of the methodology and conventions that will be used for the PopPK analysis to be performed on the data from the GDX-44-015 study entitled:

Gadopiclenol Pharmacokinetics, Safety and Efficacy in Pediatric Patients < 2 Years of Age Undergoing Contrast-enhanced MRI.

The PopPK AP ensures the credibility of all study findings by means of predefined data analysis plan. The modelers prepared the PopPK AP with the objective to finalize it before starting the analysis.

6 ANALYSIS OBJECTIVE

The objective of the analysis will be:

- To assess whether the PopPK model previously developed for adults and children aged 2-17 years of age for gadopiclenol is predictive of exposure for the pediatric population aged up to 23 months (inclusive);
- To update the PopPK model previously developed for adults and children aged 2-17 years of age with data obtained in pediatric population <2 years from the GDX-44-015 study;
- To search population specific covariates that can explain any difference between pediatric patients < 2 years and older patients;
- To predict PK parameters and exposure in pediatric patients <2 years receiving IV injection of gadopiclenol for Contrast-enhanced MRI;
- To simulate PK parameters and exposure in pediatric patients <2 years receiving IV injection of other doses of gadopiclenol (0.025 mmol/kg, 0.1mmol/kg).

7 STUDY GDX-44-015

7.1 STUDY OBJECTIVES

7.1.1 Primary Objective

To evaluate the pharmacokinetic profile of gadopiclenol in plasma following single intravenous injection of 0.05 mmol/kg body weight (BW) in pediatric population aged up to 23 months (inclusive) scheduled for a contrast-enhanced MRI examination of any body region including central nervous system (CNS).

7.1.2 Secondary Objectives

1. To evaluate the safety of gadopiclenol (clinical and biological) up to 3 months following single administration.

2. To evaluate the efficacy of gadopiclenol-enhanced MRI by body region (CNS, vessels and pool of others) as assessed by on-site Investigator.

7.2 SUMMARY OF STUDY DESIGN

This Phase II open-label, uncontrolled, multicenter trial is designed to investigate the pharmacokinetic (PK) profile of gadopiclenol in plasma, in pediatric population <2 years, using a population PK approach. This

approach, which allows sparse blood sampling, is selected to minimize the clinical burden to children. Blood sampling will be recommended via indwelling catheters rather than by repeated venipunctures.

Inclusion will be started using an age-down staggered approach. Three age groups are defined:

- Group 1: patients aged 3 to 23 months (inclusive)
- Group 2: patients aged 28 days to less than 3 months;
- Group 3: patients aged from birth to 27 days (term newborns).

The inclusions was initially planned to start with the oldest patients (Group 1) and end with the youngest patients (Group 3) (cf. protocol V2.0 dated 21 July 2022). However, following the protocol amendments (cf. protocol V4.0 dated 9-Oct-23) the aged-down staggered approach was discontinued to allow the inclusions in Group 3 (patients aged from birth to 27 days).

The previous age group will be completed in parallel with the start of the next group.

7.3 TREATMENTS

Investigational Medicinal Product (IMP) Name: gadopiclenol (formulation G03277.100)

Pharmaceutical form: 3 mL of sterile, clear, transparent ready-to-use aqueous solution for injection contained in vials of 10 mL.

Concentration: 0.5 M

Route and method of administration: The IMP will be administered intravenously (IV) manually or by power injector (if the desired volume can be delivered by the injector) as a bolus injection at a recommended rate of 1-2 mL/sec.

Contrast-enhanced MRI can start shortly after the injection depending on the pulse sequences used and the protocol for the examination. Gadopiclenol injection will be followed by a saline flush to ensure complete administration of the contrast.

Patients will be dosed according to their body weight (BW) on the day of MRI examination. Gadopiclenol will be administered at a dose of 0.05 mmol/kg BW (0.1 mL/kg BW).

The patient's participation starts from the signing of the Informed Consent Form by the parent at V1 (screening) and ends at V5 (3-month safety follow-up) or earlier in case of premature discontinuation.

The date of the last visit (date of the last procedure related to the visit) of the last patient undergoing the trial will correspond to the end of the trial.

7.4 STUDY POPULATION

50 patients will be included in the trial, according to the inclusion and exclusion criteria and assuming that at least 45 patients will be evaluable for the PK.

Patients will be distributed between the 3 age groups as following:

- - Group 1: at least 20 patients
- - Group 2: at least 12 patients
- - Group 3: at least 5 patients

At least 25 patients (50%) will be scheduled to undergo contrast-enhanced MRI of CNS (CNS cohort)

7.5 PK SAMPLING

The start of IMP administration is set as time point 0 (T0), and 3 blood samples will be collected per patient (one sample will be obtained during the 10-60 minutes time window, the second sample will be obtained during the 2.0-4.0 hours' time window and the third sample will be obtained during the 6.0-8.0 hours' time window post-injection). For each patient, within each time window, the sampling time points will be allocated by randomization, as per the Table 1 below, at the inclusion visit, allowing a good estimation of PK parameters. Exact time of sample collection will be recorded.

Table 1 Sampling time points randomly allocated.

Time Window	Sampling time within Time Window (allocated by randomization)
W1: 10 min to 60 min post-injection	**W1.1:** 10 min to < 25 min post-injection
	W1.2: 25 min to < 35 min post-injection
	W1.3: 35 min to < 45 min post-injection
	W1.4: 45 min to 60 min post-injection
W2: 2.0 hours to 4.0 hours post-injection	**W2.1:** 2.0 hours to < 2.5 hours post-injection
	W2.2: 2.5 hours to < 3.0 hours post-injection
	W2.3: 3.0 hours to < 3.5 hours post-injection
	W2.4: 3.5 hours to 4.0 hours post-injection
W3: 6.0 hours to 8.0 hours post-injection	**W3.1:** 6.0 hours to < 6.5 hours post-injection
	W3.2: 6.5 hours to < 7.0 hours post-injection
	W3.3: 7.0 hours to < 7.5 hours post-injection
	W3.4: 7.5 hours to 8.0 hours post-injection

Further to the change in protocol V4 (dated 9 October 2024), the collection of PK samples from the same line used for the IMP injection, or alternatively the use of a capillary specimen (for example heel-pricks or finger pricks), in the event of any difficulties to place and/or maintain the peripheral intravenous line into a vein, were allowed.

8 STUDY DATA

8.1 JUSTIFICATION FOR THE NUMBER OF SUBJECTS

The sample size was determined in order to optimize the characterization of gadopiclenol pharmacokinetics, with a good precision of parameters, in pediatric population through popPK modelling, which is the study primary objective. Sample size determination was coupled with evaluation of the PK sampling scheme recommended by FDA for the evaluation of the PK of Dotarem® in the same population of pediatric patients aged between 0 and 2 years[1].

Simulations were performed in order to evaluate the performance of the design and the sample size, using gadopiclenol popPK model for adult and children aged between 2 and 17 years, refined to account for renal maturation in pediatric population <2 years.

The design evaluation was performed for a sample size of 45 subjects evaluable for the primary criteria, and for 40 subjects. Overall, the sampling design with either 45 or 40 subjects will allow to estimate all fixed parameters (clearances and volumes) with an excellent precision (Relative standard error (RSE) <=20%). The between subject variability for clearance (CL) and residual error will be also very well captured (RSE<30%). Only the variability for the central volume of distribution could be poorly estimated if the pediatric population <2 years data cannot be combined with other data (stand-alone pediatric population <2 years model).

With only 3 samples to be taken by pediatric population <2 years, it is anticipated that inter-individual variability (IIV) on volumes of distribution could not appropriately estimated, even with larger sample size. This is not considered as a relevant issue invalidating the sampling design, because this variability is of limited interest as far as the IIV for CL is correctly estimated. Increasing the sample size will moderately improve the estimation of the IIV on volume of distribution, in case of pediatric population <2 years data cannot be pooled with other data collected in adult, children and adolescents.

Assuming that about 10% of patients included in the trial will not be evaluable for the primary criteria, a sample size of 50 patients, in agreement with the pediatric plans (PIP/PSP), will allow to achieve the study objectives.

8.2 DEFINITION OF POPULATION

8.2.1 Population Analysis Set

8.2.1.1 GDX-44-015

Patients from the GDX-44-015 Per protocol population will be considered for the population PK analysis.

The Per Protocol Set (PPS) will include all patients in the Safety Set without major deviations likely to impact the population PK model.

Major deviation is defined as a deviation having an impact on the primary criteria. At minimum following protocol deviations will be stated as major in the trial:

- Patient not administered with gadopiclenol
- No plasma PK sample was obtained
- Concomitant treatment or procedure (e.g., diuretics, clinically significant blood loss or blood
- transfusion) that may alter gadopiclenol pharmacokinetic parameters
- All information regarding time of injection and times of PK sampling is missing.

8.2.1.2 GDX-44-003, GDX-44-005, GDX-44-007 and GDX-44-013

The reference population will be the non-Japanese adults with normal renal function, non-Japanese adults with renal impairment, non-Japanese children and Japanese Healthy Volunteers (HV) from GDX-44-003, GDX-44-005, GDX-44-007 and GDX-44-013 studies, respectively, used to set up gadopiclenol popPK model.

In this analysis, subjects from GDX-44-003, GDX-44-005, GDX-44-007 and GDX-44-013 studies, who received gadopiclenol, regardless of the quantity, providing that the amount received and the time of injection were documented, and for whom at least one blood sample for PK with proper timing information was available, were to be included.

In GDX-44-003 study, two populations were investigated. Study Part I was performed in healthy volunteers aged from 18 to 42 years, while Study Part II was performed in patients with brain lesion aged from 25 to 58 years. No difference was elicited between these populations in previous analyses, therefore the population of subjects from GDX-44-003 study was considered homogeneous[2].

In GDX-44-005 study, 5 cohorts of subjects aged from 18 to 71 years were recruited, including healthy volunteers (cohort 1), patients with mild renal impairment (cohort 2), patients with moderate renal impairment (cohort 3), patients with severe renal impairment (cohort 4) and with patients with end stage renal disease (ESRD) (cohort 5). Of note, ESRD patients were not included in the PK analysis[3].

In GDX-44-007 study, pediatric patients aged 2 to 17 years were recruited into 3 predefined age groups (12-17, 7-11 and 2-6 years)[4].

In GDX-44-013 study, healthy male and female Japanese subjects between 20 and 60 years old were recruited[5].

Few patients are excluded from the PopPK analysis, as presented in the bioanalytical and PK report from each study:

- In the GDX-44-003 study, subject 014 from study part I (dose level 0.025 mmol/kg) was excluded from the analysis set due to incorrect dose injection followed by non-quantifiable plasma samples as well as patient 140 (dose level 0.1 mmol/kg) from study part II due to misadministration.
- In the GDX-44-007 study, 3 PK profiles (children PPD) and the first time point of 8 children (PPD ; PPD were considered as noteworthy outliers with unlikely PK profiles in the previous analysis and were not considered in the reference population analysis set. However, the final model was re-run with those children included in the analysis set as a sensitivity analysis.
- In the GDX-44-013 study, subject PPD was excluded due to major deviation from the clinical protocol.

No subject was excluded from the GDX-44-005 study.

8.3 ANALYSIS DATASETS

The analysis dataset will be created and formatted according to NONMEM requirement using SAS®.

The sponsor will provide values of gadopiclenol plasma concentrations measured, time of sampling, dose amount and information about compliance (date and time of dosing).

Moreover, subjects' demographic characteristics and any other data that could contain information valuable for the popPK model (covariates for example) will be provided to PhinC Development.

All data used for the NONMEM analysis dataset will be taken from the SDTM database. Data conversion to NONMEM structure will be performed using SAS® programming.

NONMEM dataset will be assembled using the actual date and time of all recorded administration and of samples of gadopiclenol.

A quality control (QC) will be performed between the source data and the final analysis dataset. Once controlled, the SAS® analysis dataset will be converted into an ASCII file readable by NONMEM and further used for PopPK analysis.

The inclusion of Japanese healthy volunteer data from GDX-44-013 study in this model will be performed later when the study on Japanese pediatric patients data will be completed and their data available for updating the model.

8.3.1 Concentrations

All plasma concentrations of gadopiclenol with their actual date and time of sampling will be used for the popPK model.

Theoretical relative sampling times will be included in the dataset for reporting purpose only.

No concentration will be excluded a priori from the analysis unless the sampling date and/or time is missing and cannot be reasonably imputed by its theoretical value or when no dosing information (amount and time) before the sampling is available.

Exception will be made for excluded PK profiles from GDX-44-007 study (described in Section 8.2.1.2) which were considered as noteworthy outliers with unrealistic PK profile likely to bias the parameters estimation. They will be excluded from the analysis, consistently with previous analyses.

8.3.2 Dosing events and design variables

Dosing information will be included in the database using the actual date and time of administration as well as the actual amount of drug administered. Dosing events will be entered in NONMEM dataset using the appropriate flag variables (EVID=1 and MDV=1).

8.3.3 Covariates

Continuous and categorical covariates may be used through the modelling to investigate their effect on PK parameters.

Categorical covariates will be handled as indicator variable for presence (covariate=1) or absence (covariate=0) for the factor.

Covariates (see section 9.5) will be fully defined in the data definition file, specifically the coding used for categorical covariates.

8.3.4 Missing data

8.3.4.1 Dependent variable

Some distinction will be made between concentrations non-available due to values below the limit of quantification (BLQ) and missing data for any other reason (missing sample, not analyzed sample, premature discontinuation, etc.).

The number of BLQ data will be examined before the analysis. If BLQ samples represents no more than 15% of the total samples and does not appear to be dependent to a structural covariate, then BLQ values will be removed from the analysis dataset (M1 method as documented by Beal [6]). If BLQ samples represent more than 15% of the total samples or appeared to be dependent to a structural covariate, an alternative method will be considered (M3 or M4 described by Beal).

Missing PK concentrations data, for any other reason will not be replaced and will be set to missing in the analysis dataset using the missing dependent variable (MDV=1).

8.3.4.2 Covariate

For any covariate, continuous or categorical, if values are missing for more than 15% of the subjects, the covariate will be omitted from the analysis.

As a general rule for missing baseline covariates, unless considered inappropriate, the population median baseline value for continuous covariates, or the most conservative category for categorical covariates will be imputed.

For time varying covariates, if any, data will be imputed within individual using the last observation carried forward (LOCF) method.

8.3.4.3 Design variables

Observations (or subjects) with missing information on amount of drug administered, dosing date or time and sampling date or time will be excluded unless strong evidence can determine that drug was administered (*e.g.* confirmation by the Investigator that the drug was really administered either in a monitoring report or the data-review report). In that case theoretical date and time of dosing or sampling will be used.

8.3.5 Data cleaning and detection of outliers

An outlier is an aberrant value that significantly deviates from the rest of the values.

Data review will be performed to identify potential errors in the data variables that will be used for the popPK analysis. Errors of this type would include, but not be limited to, missing data, inconsistencies between scheduled PK sampling times and actual sampling times, obvious suspected errors in recording of dates and/or times (resulting in negative estimates of actual times, for example), physiologically unreasonable covariate values, and unit of measurement errors.

Outlier sampling detection in PK profiles is mainly based on graphical representation as individual spaghettis plots by relevant groups. In sparsely sampled PK data, population and individual weighted residuals will also considered in the identification of potential outliers.

A large deviation of a unique observation from adjacent observations within a PK profile, or an absolute value above 6 of weighted residuals justifies a point review. If inconsistencies are confirmed (i.e.: unphysiological value, etc.) the point, as an outlier, will be excluded of the analysis or included in a sensitivity analysis.

If the entire individual PK profile is unreliable to the expected PK behavior, and no other factors (co-administration of other drugs, noncompliance, extreme covariate values, etc.) could definitely explain the deviation, the entire data from the subject will be excluded, or included in a sensitivity analysis, to prevent potential bias into the analysis.

9 MODEL DEVELOPMENT

PopPK parameters will be estimated by non-linear mixed effect modelling using NONMEM. Mixed effects models describe the influence of both fixed effects and random effects. The random effects are typically used to capture the variability which can be split in residual variability (error) and between subject variability.

The population model will be defined by 4 basic components:

1. The structural popPK model components, which defines the PK parameters and describe the plasma concentration-time profiles of gadopiclenol.
2. The inter-individual error model component, which describes the inter-individual variation (IIV) in PK parameters after correction for fixed effects.
3. The residual error model component, which describes the underlying distribution of the error in the measured concentrations.
4. The covariate model component, which describes the influence of fixed effects (*i.e.*, demographic factors) on PK parameters.

As a popPK model for gadopiclenol was already developed[5], this model will be used as starting point for the pediatric population (< 2 years old) with the objective to enrich and update the existing model if possible.

9.1 SEQUENCE OF PLANNED ANALYSIS

The popPK model will be developed according to the following strategy:

1. Preliminary checks will be performed to assess whether the existing model[5] is predictive of data collected in pediatric patients <2 years. If it is the case, data from these pediatric patients will be

added to previous data in order to update the existing model, otherwise, only pediatric population <2 years data will be used for model development

2. On the selected dataset (only pediatric population <2 years or pediatric population <2 years added to previous data), selection of the simplest structural model, which predicts the plasma concentrations as a function of time and dose, based on smallest objective function and by the pattern in the residual plots. The best estimation method, the most appropriate IIV models, and the residual error model, will be identified. The resulting model is called BASE. In this model, population specificities will be accounted for as structural covariates.
3. Graphical exploration of the covariates: between individual covariates and post-hoc (FO) or conditional (FOCE) parameter estimates and between covariates and conditional weighted residuals (CWRES).
4. Determination of the covariate model using a backward deletion process:
    a. Univariate analysis (covariates are added only to parameters having η in BASE).
    b. Multivariate analysis: all selected covariates are added together, the model is fit to data and a new value of objective function (OFV) will be obtained and considered as a reference called FULL model
    c. Selection of significant covariate to obtain the FINAL model

9.2 *PRELIMINARY CHECKS*

In order to check if the existing model is predictive of data collected in pediatric population <2 years, some preliminary checks will be performed.

First, gadopiclenol concentrations in pediatric patients <2 years will be simulated using the existing model (see model definition in Section 9.3) and actual patients' settings (dose, sampling, characteristics). A prediction-corrected performance visual checks (pcVPC) approach will be used, simulating 1000 replicates of pediatric patients <2 years and plotting the distribution of these simulated concentrations with the actual measured concentrations. The pcVPC approaches are defined in Section 10. The measured concentrations should be fairly distributed within the simulated distribution.

In a second step, the existing model will be applied to pediatric population <2 years data with model's parameters fixed to the final estimates obtained in previous data. The variability terms (IIV and residuals) will be estimated. Diagnostic plots (as defined in Section 9.8) will be used to assess model misspecification.

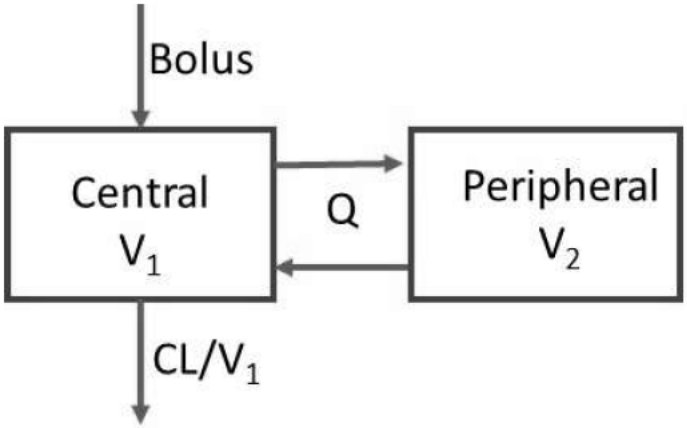
Should any interim evaluation need to be performed during the course of the study to determine if exposure in any group of pediatric patients <2 years is as expected, the first step based on pcVPC will also be used for this purpose.

9.3 *STRUCTURAL PHARMACOKINETIC MODEL*

The population PK model selected on previous data was a two-compartment model with elimination from the central compartment. The model was parameterized in terms of clearance (CL), central volume of distribution (V_1), inter-compartment clearance (Q) and peripheral volume of distribution (V_2). All parameters were scaled to body weight using fixed allometric rules. The CL was also scaled to eGFR with a power model for pediatric population and a Gompertz function for adult population. Ethnic population covariate was

applied on all parameters. Exponential models were used to describe the inter-individual variability on CL, V_1 and V_2 and a proportional model was considered as error.

Figure 1 Structural Gadopiclenol Population PK model



Further to the submission of gadopiclenol application to health authorities, it was requested by EMA to replace the two equations used to estimate the influence of eGFR on CL of adults and children by a single equation based on serum creatinine (Screat) instead of eGFR. The model used for the application was the one model built on studies GDX-44-003, GDX-44-005 and GDX-44-007 (i.e. without study GDX-44-013 in Japanese volunteers).

Such model was obtained and the relationship between Screat and CL was best described with a 3 parameters Gompertz function as follows:

$$CL_i = \theta \times (1 - A \times \exp(-\exp(-B \times (Screat - C)))) \times \exp(\eta)$$

Where A=asymptote value, B=growth rate and C=inflexion point.

Parameters estimates are presented in Table 2.

Table 2 Gadopiclenol population PK model parameters estimates from the model refined for EMA submission and using Serum creatinine as covariate to describe renal function impact on CL

Parameter	Estimate (%RSE)	95% CI	Variability (CV%) Correlation (R%)
$CL(L/h) = \theta_1(Weight/70)^{0.75}*(1-\theta_5*EXP(-EXP(-\theta_6*(Screat-\theta_7))))*EXP(\eta_1)$			
θ_1: CL typical value	5.61 (2.44)	(5.34;5.88)	
θ_5: Asymptotic (maximal) effect of Screat on CL	0.869 (1.28)	(0.847;0.891)	
θ_6: growth rate of CL	0.0334 (12.8)	(0.025;0.0418)	
θ_7: inflexion point of adults CL	110 (3.37)	(103;117)	
η_1 (IIV CL)	0.0450 (13.3)	(0.0333;0.0567)	CV=21.2%
$Q (L/h) = \theta_2(Weight/70)^{0.75}*EXP(\eta_2)$			
θ_2: Q typical value	4.15 (8.31)	(3.47;4.83)	
η_2 (IIV Q)	0.285 (28.0)	(0.128;0.442)	CV=53.2%
$\eta_{2,1}$ (cov CL, Q)	0.043 (39.5)	0.00968; 0.0763	R=38%
$V_1 (L) = \theta_3(Weight/70)*EXP(\eta_3)$			
θ_3: V_1 typical value	7.55 (2.94)	(7.11;7.99)	
η_3 (IIV V_1)	0.0724 (18.2)	(0.0465;0.0983)	CV=26.9%
$\eta_{3,1}$ (cov CL, V_1)	-0.00177 (350)	-0.0139; 0.0104	R=3.1%
$\eta_{3,2}$ (cov Q, V_1)	-0.116 (28.3)	-0.180; -0.0517	R=-80.8%
$V_2 (L) = \theta_4(Weight/70)*EXP(\eta_4)$			
θ_4: V_2 typical value	4.80 (4.96)	(4.33;5.27)	
η_4 (IIV V_2)	0.203 (17.6)	(0.133;0.273)	CV=45.1%
Residual error			
ε_1: proportional component	0.0206 (5.87)	(0.0182 ;0.0230)	CV=14.4%
OFV: 9422.311 - Run number EMA8 Condition Number: 92.2			

This model will be considered as starting point for the modeling including pediatric patients (<2 years old) during structural model refinement. Depending on the preliminary checks, it will be either updated and refined after including pediatric patients <2 years to the existing dataset or considered as initial setting for building a pediatric population <2 years model. The inclusion of Japanese healthy volunteer data from GDX-44-013 study in this model will be performed later when the study on Japanese pediatric patients data will be completed and their data available for updating the model.

Once the structural model will be defined, the residual error model will be refined and finally the IIV will be introduced on the PK parameters for which the estimation of the variability can be supported by the data. At this step the error models will be diagonal (no covariance between variance components will be included).

The selection of the most parsimonious structural model with appropriate IIV and residual error will be called the BASE model.

9.4 *ERROR MODELS SPECIFICATION (RANDOM EFFECTS)*

Total variability (model errors) will be split as inter-individual and intra-individual components.

In population modelling, each subject is assumed to be sampled from a representative population. Thus, the individual PK profiles can be considered as a random realization of a population PK model, which by extension is equivalent to consider that each individual profile is obtained by a subject specific random realization of each parameter of the model.

The model parameters are thus considered as random effects having a mean value (or typical value) and a variability. These variabilities are the inter-individual variability component.

Other sources of error (noise, error or measurements, model misspecification, etc.) are included in the residual error term and associated with the intra-individual variability component.

The objective of the population PK modelling is to obtain estimates of the typical values and the variability of the parameters, as well as of the residual error.

9.4.1 Models for inter-individual variabilities (IIV)

Let θ_i refers to the parameter value in the i^{th} individual, θ_{TV} is the typical value of the parameter in the population, and η is a Gaussian random variable with a mean of 0 and a variance of ω^2.

Two models for IIV can be considered:

1. The exponential model:

$$\theta_i = \theta_{TV} e^{\eta_i}$$

The exponential model is useful for a lognormal distribution. In that case θ_{TV} denotes the median of the distribution.

2. The additive model:

$$\theta_i = \theta_{TV} + \eta_i$$

The additive model is a standard Gaussian model with constant standard deviation (SD).

As far as possible, the exponential model will be considered for PK parameters in order to ensure strictly positive values. However, in some circumstances, the additive model could provide a better fit and should be considered. The distribution of the random terms will be investigated to determine the best model.

9.4.2 Model for residual variability

Three different models of residual variability will be tested on measurable plasma concentrations:

The additive error model: $Y=f+\varepsilon$

The multiplicative error model: $Y=f.(1+\varepsilon)$

The mixed error model: $Y=f+\varepsilon_1+f.\varepsilon_2$

Where Y are the observed concentrations, f are predicted concentration, and ε, ε_1 and ε_2 are random variables with a mean of 0 and variance respectively of σ^2, σ_1^2 and σ_2^2.

Residual variability will be expressed as a coefficient of variation (CV) for multiplicative error model and SD for additive model.

9.5 COVARIATE MODELS

The objective of the inclusion of significant covariates in a model can be:

- explain the random variability (and thus reduce IIV)
- Understand causes of variability and apply the knowledge
- Improve the predictive performance of the model for further use

Let:

θ_{TV} be the typical value for a PK parameter (*e.g.* CL/F, V/F, etc.)

θ_{pop} be the population value for this parameter

COV_i be a covariate:

If COV_i is continuous,

If COV_i is categorical COV_i=1 means presence of the characteristic, COV_i=0 means absence of the characteristic.

θ_i be the fixed parameter associated to the covariate.

Commonly used functional form for continuous covariates are:

$$\theta_{TV} = \theta_{pop} \times \left(\frac{COV_i}{Median_{Cov_i}}\right)^{\theta_i} \text{ (power)}$$

or

$$\theta_{TV} = \theta_{pop} \times \exp\left(\theta_i (COV_i - Median_{Cov_i})\right)$$

The effect of categorical covariates will be evaluated using the following model :

$$\theta_{TV} = \theta_{pop} \times \exp(\theta_i \times COV_i) \text{ (exponential)}$$

The nature of the functional form for each (covariate, parameter) pair will be determined using a graphical approach involving individual predictions if the shrinkage value of the random effect associated to the parameter is limited (≤ 30%).

When using the FOCE method, if the shrinkage is >30%, the conditional individual values are considered to shrink toward the corresponding observations and to be uninformative at the individual level. In that case, the graphical approach should be used with caution and all structural forms will be considered and the form improving the most the OFV will be selected.

The graphical exploration will consist on scatter plots with smoothing curve for continuous covariates and box-plots for categorical covariates between each covariate and:

- Individual parameters estimated from the BASE model;
- Weighted residual from the BASE model.

The model of parameters including covariates will depend on the shape of the relationship evaluated during graphical exploration.

The effects of the following covariates on model parameters will be considered a priori:

- Influence of age on clearance and volume of distribution,
- Screat at screening on clearance ,
- gender on clearance and volume of distribution.

Only covariates that were measured or reported in at least 15% of the population will be considered for the covariate model.

As in the previous model[5], ethnic effect will be included on each parameters in the structural model, the influence of Screat will be included on the clearance in the structural model and the body weight will be included in the structural model using standard allometric scale:

$$CL_i = CL_{pop} \times \left(\frac{Weight_i}{70}\right)^{0.75}$$

$$V_{1_i} = V_{1_{pop}} \times \left(\frac{Weight_i}{70}\right)$$

$$Q_i = Q_{pop} \times \left(\frac{Weight_i}{70}\right)^{0.75}$$

$$V_{2_i} = V_{2_{pop}} \times \left(\frac{Weight_i}{70}\right)$$

9.6 *STATISTICAL MODEL SELECTION*

Once the BASE model was obtained, influence of predefined covariates will be investigated first using a univariate analysis.

The following procedure will be used for the univariate analysis:

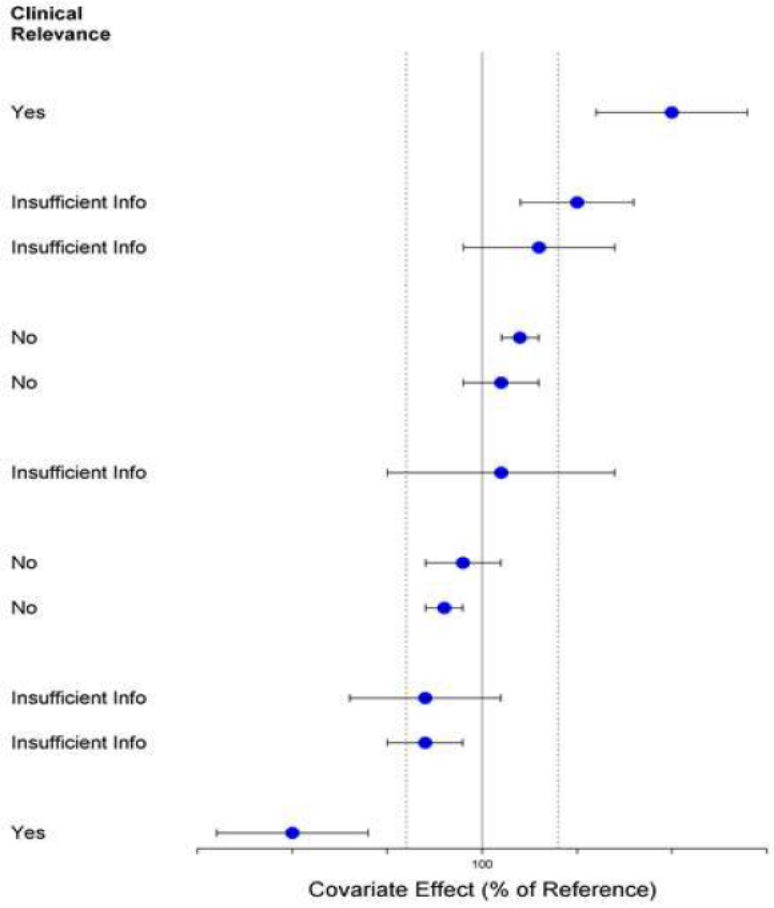
- One covariate effect on a single model parameter is included in the BASE model per run;
- Take care not to include several covariates that are markers of the same feature (*e.g.* weight and BMI) in order to avoid collinearity. Choose the best;
- Addition of a covariate is significant if the LRT gives a p-value < 0.05 (*i.e.* ΔOFV ≥ 3.84);
- Repeat these steps with all covariates and parameters suspected to be affected by the covariates;
- Rank the covariates by size of effect on OFV by comparison to the base model (the largest decrease is ranked 1).

Once the univariate step is complete and covariates were selected, a backward multivariate analysis will be performed:

- Add all significant covariates selected by the univariate steps to the model and get a new OF for this FULL model;
- Proceed to a backward deletion until no covariate can be removed without significantly increasing the objective function:
    - Remove the covariates once at a time, starting with the weakest obtained by the ranking of the univariate process. Fit to the data, get the OF and compare to the OFV of the FULL model. Decide to keep the covariate in the model if the covariate is significant at the α^* level where α^* is an adjusted level insuring a maximal overall 5% type I error over all tests performed.
    - Repeat this step until all covariates are tested versus the last accepted model.
- When all covariates are tested, get the FINAL model and compute 95% confidence intervals (CI) on the parameters. 95%CI will be computed as $\theta \pm 1.96 \times SE(\theta)$.

Moreover, in order to facilitate the interpretation of the importance or the potential clinical relevance of a covariate instead of relying only on statistical significance, forest plots will be performed with the statistical model including all significant covariates, and it will consist of evaluating the effect of each covariate comparing the 95% confidence interval (CI) of the covariate against a predetermined threshold (5^{th} and 95^{th} percentile, in case of continuous covariates). If the 95% CI is outside the predetermined range, the influence of the covariate can be considered sufficiently large, *i.e.* may be potentially of clinical relevance. If the 95% CI includes 1 (or 100%), the influence of the covariate is statistically non-significant. If the 95% CI is within the range and excludes 1 (or 100%), the influence of the covariate is statistically significant but not sufficiently large to have a potential impact in the clinical context. In other cases, there may be not enough information to conclude about the effect of a covariate, as summarized in Figure 2.

Figure 2 Tested relevance of covariates in the model



The range of 0.80 to 1.25, the same as the bioequivalence threshold will be chosen in this analysis. Here it will be called the range of sufficiently large covariate effect because covariate testing will be performed on all parameters showing correlation with studied covariates.

After this step, the final model could be determined.

9.7 *ESTIMATION METHOD AND MODEL ACCEPTANCE*

Due to the rich sampling nature of the data the FOCE method (with η-ε interaction) will be the preferred method *a-priori*.

At each step of the model building, intermediate models will be accepted if:

- Minimization is successful.
- Covariance step finishes without warning message.
- Number of significant digits on parameters is superior or equal to 3.
- Correlation between any 2 parameters (θ, η or ε) is inferior to 0.95.
- Absolute values of gradients at last iteration are inferior to 100 but > 0.001 in order to avoid local minima.

For the final model, in addition to these criteria, the following will be evaluated:

- 95%CI of estimates excludes 0. If 0 is included within the 95%CI, this will lead to exclusion of the corresponding parameter from the model unless it will be part of the structural PK model;
- Over-parameterization will be assessed using the condition number for which a value exceeding 1000 is indicative of severe ill-conditioning.

9.8 *MODELS EVALUATION AND GOODNESS OF FIT*

The following diagnostic and goodness of fit plots are applicable at each step of model building:

- Population Weighted Residuals and NPDE versus Population Predicted Concentrations (WRES vs PRED), with a null intercept horizontal line and a trend line;
- Population Weighted Residuals and NPDE versus Time/Time after last dose, with a null intercept horizontal line and a trend line;
- Individual Weighted Residuals versus Individual Predicted Concentrations (IWRES vs. IPRED) , with a null intercept horizontal line and a trend line;
- Individual Weighted Residuals and Absolute Individual Weighted Residuals versus Time/Time after last dose, with a null intercept horizontal line and a trend line;
- Concordance plot of Observed Concentrations versus Population Predicted Concentrations (DV vs PRED), with the line of identity and a trend line, in linear and log scale;
- Concordance plot of Observed Concentrations versus Individual Predicted Concentrations (DV vs IPRED), with the line of identity and a trend line, in linear and log scale;
- Histograms or Q-Q plots of the Population Weighted Residuals (WRES), Individual Weighted Residuals (IWRES) ;
- Histograms or Q-Q plots of the empirical Bayes Estimates (EBEs) of the parameters and/or random effects (η);
- Scatter plot matrix of parameters EBEs.

For the covariate models, the following plots will be provided:

- Index plots of EBEs of random effects (η) against covariates;
- Index plots of residuals (WRES) against covariates.

For the final model, the following plots will be added:

- Individual plots displaying on the same graph (1 figure/panel by subject) the observed, the individual predicted and the population predicted concentrations over time.

Goodness of fit (GOF) plots can be stratified by dose, or any other condition that is deemed relevant (such as health status for example).

Only goodness of fit plots for the BASE and FINAL model will be compiled for inclusion in the popPK dedicated document for results, all other intermediates GOF plots could be generated on request but will not be saved.

For the FINAL model, quality of individual PK parameters estimates will also be assessed using shrinkages.

10 EVALUATION OF PREDICTABILITY AND STABILITY OF THE MODEL

Evaluation of predictability and stability of the FINAL model will be performed using prediction-corrected performance visual checks (pcVPC). The pcVPC were shown to be a more powerful diagnostic tool than classical VPC to detect important model misspecifications[7]. Especially because they aims to correct for the differences within a time bin coming from independent variables such as population or time difference within a sampling window.

The pcVPC will be computed and displayed as follow:

- Like for classical VPC, perform a large number of replication (N ≥ 1000) of the original dataset using the parameters estimated in the FINAL model through Monte Carlo (MC) simulations.
- pcYij= Yij.(PREDbin / PREDij)

  where:

  Yij = observation or simulated prediction for the i^{th} individual and j^{th} time bin

  pcYij = prediction-corrected observation or simulated prediction

  PREDij = typical population prediction for the i^{th} individual and j^{th} time bin

  PREDbin = median of typical population prediction for the specific bin of independent variable
- The 5%, 50% (median) and 95% percentiles of the original plasma concentration will be calculated and presented graphically over time.
- Simulation-based 90% prediction intervals (defined as the interval between the 5% and the 95% percentile from simulated datasets) will be obtained by time point for the 5%, the median and the 95% percentiles and presented graphically as bands.

A line for the observed median or 5%-95% percentiles moving outside its respective simulation-based prediction interval denote a model misspecification regarding central tendency (median) or variability (5% - 95% percentiles).

11 DERIVED VARIABLES

GFR at screening in pediatric population <2 years will be estimated using bedside Schwartz equation:

$$eGFR\ (mL/min/1.73m^2) = \frac{0.413 \times height\ (cm)}{Serum\ creatinine\ (mg/dL)}$$

By convention, subjects with serum creatinine value BLQ at screening will be imputed a value of eGFR calculated with the LLOQ value of creatinine.

The following PK parameters will be derived from the final population PK model:

Area under the curve:

$$AUC_{0-\infty} = \frac{dose\ administered}{CL}$$

Terminal half-life (assuming a 2-compartment model):

$$t_{1/2\beta} = \frac{\ln 2}{\beta}, where\ \beta = \frac{1}{2}\left[k_{12} + k_{21} + k_{10} - \sqrt{(k_{12} + k_{21} + k_{10})^2 - 4k_{21}.k_{10}}\right]$$

where:

k_{12} is the rate constant from compartment 1 to compartment 2;

k_{21} is the rate constant from compartment 2 to compartment 1;

k_{10} is the rate constant of elimination from compartment 1.

12 SIMULATIONS

The final population PK model will be used to simulate gadopiclenol concentrations at 10 (C_{10}), 20 (C_{20}) and 30 (C_{30}) min after injection as well as AUC, at the doses 0.025 mmol/kg, 0.05 mmol/kg and 0.1 mmol/kg for each population.

The final dataset will be used for the simulations and 1000 replicates of this dataset will be obtained to determine the distribution of C_{10}, C_{20}, C_{30} and AUC.

These exposures variables will be compared descriptively by age groups (adults, 12-17, 7-11, 2-6 years and <2 years), by ethnic group and by health status, using descriptive statistics (2.5th percentile, median, 97.5th percentile, geometric mean and CV) as well as graphically using box-plots.

12.1 SIMULATION IN CASE OF TERMINATION OF THE STUDY BEFORE COMPLETION OF THE RECRUITMENT

In the event that recruitment cannot be completed as planned at the end of the study, the exposure and PK parameters in non-recruited age groups will be determined by simulation.

The modeling steps (preliminary checks, model upgrade / refinement and validation) with the data available at end of study will be performed as specified in Section 9 and 10.

The refinement of the model will focus specifically on the impact of Screat on elimination parameter since it is known that renal function is not mature before 1 year old[8],[9],[10] and the current relationship does not account for the maturation in youngest patients.

In order to simulate a realistic pediatric (<2 years) population of patients in terms of association between gender, age, weight and SCreat levels, the 45 patients from the study DGD-44-063[(1)] will be used.

For each age group not recruited and to be simulated, two hundred individuals (100 female and 100 male) will be sampled, with replication, from the DGD-44-063 dataset.

The PK exposure parameters (C_{10}, C_{20}, C_{30} and $AUC_{0-\infty}$) for the dose 0.05 mmol/kg will be simulated for these patients from the popPK model obtained after inclusion of the recruited patients.

The same simulations will be performed for all other paediatric age groups and for adults with normal renal function by resampling, for each age group, subjects from the available data (including GDX-44-015 for age group recruited, GDX-44-007 for pediatric subjects above 2 years old, GDX-44-003 and GDX-44-005 for adults with normal renal function.

The distribution of simulated parameters will be summarized graphically using box plots by age group. Moreover, 5th, 25th, 50th (median), 75th and 95th percentiles will be tabulated by age group.

The PK exposure parameters simulated from the refined model will be compared to those simulated from a model where the maturation of renal function is based on post-menstrual age (PMA) instead of Screat[(10)].

The maturation function described by Rhodin *et al*. was used to describe the maturation of the renal fraction of elimination (MF_{renal}), as shown in the following equation:

$$MF_{renal} = \frac{PMA^s}{PMA_{50}^s + PMA^s}$$

Where:

- PMA is the post-menstrual age, calculated as the sum of 40 weeks gestational age (assuming a standard gestational age), plus post-natal age;
- *s* is the sigmoidicity factor (*s*=3.4);
- PMA_{50} is the PMA at which MF_{renal} reaches 0.5 (47.7 weeks).

Therefore, for the simulations of gadopiclenol concentrations in infants, the clearance term in Table 2 will be replaced by:

$$CL = \theta_1 \times \left(\frac{Weight}{70}\right)^{0.75} \times \frac{PMA^{3.4}}{47.7^{3.4} + PMA^{3.4}}$$

The PK exposure parameters (C_{10}, C_{20}, C_{30} and $AUC_{0-\infty}$) for the dose 0.05 mmol/kg will be simulated for the same populations and age groups resampled as described above and will be presented in the same manner. Alternative doses could be simulated if necessary.

The simulation workflow is summarized in Table 3.

Table 3 Simulation workflow

Reference model for simulation	Current model with SCreat level as covariate to account for renal function impact on CL, refined with available pediatric data from study GDX-44-015 available at the time of the analysis.
Population simulated	Age groups not recruited when GDX-44-015 available is terminated
Reference population	Other pediatric age groups (including children above 2 years old) with normal renal function. Adults with normal renal function
Method for simulation of population	Resampling (with replacement) from existing data base
Simulated data	Concentrations at time 10, 20 and 30 minutes after injection Individual CL AUC0-∞ derived from individual CL
Simulated doses	0.05 mmol/kg
Sensitivity analysis	Same simulations performed with alternate model of maturation of renal function based on PMA (Rhodin et al.)
Method for comparison of simulated data	Graphical display (box-plots) and descriptive tables for distribution of simulated parameters by age group

13 DISPLAY OF RESULTS AND CONTENTS OF THE REPORT

13.1 DESCRIPTION OF THE DATA

The data used for the population will be described in the report using the following information:

- Total number of subjects entering the analysis, overall and by age group;
- Total number of concentrations used in the analysis, overall and by age group;
- Total number of missing concentrations, including BLQ, overall and by age group;
- Subjects removed from the analysis listed with relevant subject characteristics and reason for withdrawal;
- Summary of demographic characteristics: descriptive statistics (N, mean, SD, minimum (Min), median, and maximum (Max)) for continuous variables and frequencies for categorical covariates, overall and by age group;
- Descriptive statistics of concentrations, by time window, including number of observations available, number of observations BLQ or missing, mean, SD, GM, CV, Min, median, and Max;
- Boxplot of concentrations by time window in natural scale and log scale;

- Individual scatter plots in natural scale and log scale;
- Subjects considered as outliers specified with all relevant data available

13.2 *BASE MODEL*

Only outputs for the relevant steps will be included in the Appendix, other intermediate run outputs will be stored and kept on the network. However, all run will be summarized in a run record describing any major decisions and including an overview of the steps taken during the model development.

The run record will include a brief description of the run, the objective function value, if the model converged successfully, the parameter estimates with their standard error. If the analysis dataset changes during the course of the analysis, the modification must be documented in the run record.

All parameters estimated in the BASE model will be presented in a table together with their standard errors and their confidence intervals. Inter-individual and residual variability models will also be reported.

GOF plots as defined in Section 9.8 will be included in the report.

13.3 *COVARIATE SELECTION AND FINAL MODEL*

Plots generated to screen for potential covariate relationships will be provided in the report (for example individual estimates of parameters versus potential covariates).

The covariate model building steps will be presented in a separate run record, displaying covariates that will be included in the FINAL model and those that were tested but not retained, together with the criteria on which the decision was based (ΔOF). A run record will be provided for the covariate selection.

The results for the FINAL model will be presented in a table together with the standard errors and the confidence intervals of the parameters estimates (model parameters, covariates and variability parameters).

GOF plots as defined in Section 9.8 will be included in the report.

The NONMEM input and output files for the BASE and FINAL models will be provided in an appendix.

13.4 *MODEL EVALUATION*

Figures for pcVPC will be presented in the report.

14 SOFTWARE USED

SAS® software V9.4 will be used for:

- Structuring the analysis dataset from the source data (bioanalytical and clinical data base) to a format suitable to NONMEM;
- Produce graphs;
- Produce summary tables (*e.g.* description of the data, numerical PPC, etc.).

NONMEM version 7.4 will be used for:

- PopPK modelling;
- Simulation of data from the FINAL model for PPC;

- NONMEM will be used through PDx-POP version 5.0 interface.

R software V4.0.5 will be used for:

- Produce graphs;
- Produce summary tables (*e.g.* model results).

15 REFERENCE LIST

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