PRODUCT: V16X	PROTOCOL/AMENDMENT **V2**
REV/OPS ID NO: NIS104141	NIR DRC APPROVAL DATE: 6/17/2026

Prospective cohort study to assess the performance of tools to describe the Natural History of CytoMegaloVirus infection and transmission in FAMILles with children attending daycare centers in France

(CMV FAMILI study)

SPONSOR
Merck Sharp & Dohme LLC., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor)
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LIST OF ABBREVIATIONS

AE	Adverse Event
CIC	Clinical Investigation Center
CMV	Cytomegalovirus
cCMV	Congenital Cytomegalovirus
CMVi	Cytomegalovirus infection
CNIL	Commission nationale de l'informatique et des libertés
CRO	Contract Research Organization
DCC	Day care center
DNA	Deoxyribonucleic acid
ICF	Informed Consent Form
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IRB	Independent Review Board
LOD	Limit of Detection
NAb	Neutralizing antibody
PCR	Polymerase Chain Reaction
PTID	Participant identification
qPCR	Quantitative Polymerase Chain Reaction
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure

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LIST OF DEFINITIONS

Health Outcomes	Clinical events or outcomes which may be represented as diagnoses, treatment or procedures (examples include syncope, disease progression or hypoglycemia collected as study endpoints).
Primary CMV infection	Seroconversion, i.e., appearance of CMV IgG and/or IgM antibodies, using a commercial serology assay for CMV IgG and/or IgM CCI , in parents/caregivers who were CMV-seronegative at baseline.
Non-primary CMV infection	Reinfection with a different strain, or reactivation of latent CMV in parents/caregivers who were CMV-seropositive at baseline (for more information, see section 6.8.2)
CMV seroconversion	Appearance of CMV IgG and/or IgM antibodies, using a commercial serology assay(s) CCI in parents/caregivers who were CMV-seronegative at baseline.
CMV DNA detection	Detection of CMV DNA by PCR above the assay limit of detection (LOD).
Caregivers	Adults who provide regular care to the child, i.e., in blended families, the partner of the mother or father of the child who lives in the same household with the child for at least 10 days a month.

1 RESPONSIBLE PARTIES

Sponsor Study Lead	PPD Senior Principal Scientist, Epidemiology 10-12 Cours Michelet 92800 Puteaux
Supplier/Collaborator	PPD PPD PPD Clinsearch 110 Avenue Pierre Brossolette 92240 Malakoff

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Investigator(s)	PPD PPD National Reference Center for Cytomegaloviruses CHU Dupuytren, CBRS 2 avenue Martin Luther King 87042 Limoges Cedex, France
Clinical Investigation Center	PPD PPD Centre d 'Investigation Clinique Centre Hospitalier Universitaire de Limoges 2 avenue Martin Luther King 87042 Limoges Cedex, France

2 ABSTRACT

Title	Prospective cohort study to assess the performance of tools to describe the Natural History of CytoMegaloVirus infection and transmission in FAMILIes with children attending daycare centers in France (The CMV FAMILI study)
Protocol Number / Version	2.0
Date Approved for the Most Recent Protocol Version	6/17/2026
Author	PPD
Rationale & Background	To reduce the burden of congenital CMV, associated with substantial long-term morbidity, CCI [redacted]. CMV infection in adults and children is typically asymptomatic or mild and lacks specific clinical symptoms. CCI [redacted] require highly specific molecular or serologic case definitions to accurately identify primary infections. Data generated from this study will support:

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	- Validation of the refined PCR-based case definition for primary CMV infection CCI [redacted] - Improved understanding of shedding dynamics, viral load patterns, and temporal relationships between shedding and seroconversion - Characterization of primary and non-primary infections in a real-world high-transmission setting CCI [redacted]
Research Question(s) & Objective(s)	Primary Objective - To assess the performance of PCR-based case definition criteria for identifying primary CMV infection in parents/caregivers who are CMV-seronegative at baseline. Secondary Objectives CCI [redacted] - To estimate the incidence of primary CMV infection, defined as seroconversion among parents/caregivers who are CMV-seronegative at baseline demonstrated within the serology assays used in this study. - To estimate the incidence of non-primary CMV infection (see definition on page 8) among parents/caregivers who are CMV-seropositive at baseline.

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	- To describe transmission patterns between children and their parents/caregivers. Exploratory Objectives - To describe viral and immune dynamics before, during, and after primary CMV infection, using longitudinal sampling. - Among non-primary CMV infections, to distinguish reinfection (new strain) from reactivation (latent strain), using genotyping and serologic data.
Study Design	Prospective cohort study
Population	Parents and caregivers of children in day-care centers in France and their children
Variables	This study includes the following outcomes of interest: (1) CMV serostatus at baseline (adults) (2) Primary CMV infection (adults) (3) Non-primary CMV infection (see definition page 8) (adults) (4) CMV DNA detection in saliva (adults) (5) CMV DNA detection in urine (adults) (6) CMV DNA detection in saliva (children) (7) CMV DNA detection in urine (children) (8) CMV genotypes (in serum from adults who are CMV seropositive at baseline) Sociodemographic covariates: Age, sex at birth, country of birth, parity (mothers only), socioeconomic status, household size, general CMV knowledge

	Biological covariates: CMV viral load in saliva and, presence/absence of CMV DNA in each specimen, serostatus and antibody titers using commercial and CCI [redacted]
Data Sources	All data will be collected prospectively.
Study Size	1000 CMV seronegative adults are needed to achieve the primary objective. Assuming a CMV seronegativity rate of ~50% in the study population, an overall of 2000 adults will be enrolled. In addition, assuming one child per two adults, ~1000 children will also be enrolled, resulting in an overall study population of ~3000.
Data Analysis	All analyses will be descriptive or exploratory; no hypothesis testing is planned. Continuous variables will be summarized using mean, standard deviation, median, interquartile range, and range where appropriate. Categorical variables will be summarized using counts and percentages where appropriate. Time-to-event analyses will use Kaplan-Meier methods to estimate cumulative incidence where appropriate. Incidence rates will be calculated per 100 person-years, with 95% confidence intervals (CIs). Analyses will be stratified by variables of interest (e.g., sex, age, household size) where appropriate. All analyses will be conducted using validated statistical software (e.g., R).

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3 PROTOCOL REVISION TABLE

Version no	Date	Section of Study Protocol	Revision Description	NIR DRC Approval Date
<2>	6/5/2026	5. Research question and objectives	Here and in other sections “main study” was replaced by “main phase” to use consistent wording as this study contains a pilot phase and a main phase.	
<2>	6/5/2026	6.1 Study design	The informational video was removed from this section as it will not be used during the pilot study.	<Date>
<2>	6/5/2026 <Date>	6.1 Study design	In accordance with recent legal changes in France that allow e-consenting without additional CNIL approval, the ICF process was adapted to allow e-consenting in addition to hard copy. The signature process was detailed for different scenarios: parents/caregivers who attend the information meeting at the day-care and those who attend the information meeting virtually as well as the use of hard-copies and e-consenting.	<Date>

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Version no	Date	Section of Study Protocol	Revision Description	NIR DRC Approval Date
<2>	6/5/2026	6.1 Study design	A flow-chart was added, illustrating the different signature scenarios.	<Date>
<2>	6/5/2026	6.1 Study design	The attribution of an identification number was added.	
<2>	6/5/2026	6.1 Study design	It was clarified that laboratory or day-care personnel can take samples from children. This was also to make the two options consistent throughout the protocol.	
<2>	6/5/2026	6.2.1 Inclusion and exclusion criteria	"≥12 months after the screening visit" was updated to "for the school year period" to provide more flexibility as day-cares might close in August or children might not attend day-care in the summer holiday period	
<2>	6/5/2026	6.3.2 Covariates	"Attendance at National First Trimester Screening during pregnancy" was removed as a covariate as this information will not be collected during the pilot phase.	
<2>	6/5/2026	7.1 Informed consent	e-consent was added	

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Version no	Date	Section of Study Protocol	Revision Description	NIR DRC Approval Date
<2>	6/5/2026	7.1 Informed consent	Reference to deliberation was updated due to recent legal changes	
<2>	6/5/2026	Table 3	Changes were made to the sample quantities/sampling methods	
<2>	6/5/2026	Questionnaire	The questionnaire was separated from the study protocol and is now presented as a stand-alone document. Question on “parity status” was added for consistency with the collection of covariates as described in the protocol	
<Protocol Clarification Letter>	<Date>	NA	<Summary of PCL>	NA

4 RATIONALE AND BACKGROUND

Background

Cytomegalovirus (CMV) is a ubiquitous human herpes virus that is spread through contact with a variety of infected bodily fluids. CMV seropositivity among women of reproductive age ranges from approximately 25% to 95%, depending on geography and socioeconomic factors [1]. Infections in adults are usually mild or asymptomatic. However, CMV infection during pregnancy can result in congenital CMV (cCMV) infection, a major cause of neurodevelopmental disability [2]. Approximately 15-20% of infants born with cCMV infection develop permanent neurological sequelae, most commonly sensorineural hearing loss, but also microencephaly, cognitive disability, visual impairment, and infant mortality [2].

To date, there are no well-established methods to prevent congenital CMV infection, and no CMV vaccine has been licensed. Primary CMV infection during pregnancy is associated with a high risk of congenital CMV infection [3], occurring in approximately one-third of cases [4]. Although preconception immunity provides partial protection against maternal-fetal CMV transmission [5], CMV can also be transmitted to the fetus during “non-primary” maternal infection, defined as either reactivation of latent CMV or reinfection with a different strain [4] [6] [7]. Both reinfection and reactivation are known to contribute to cCMV, but their relative frequency and mechanisms remain poorly characterized [8]. Importantly, severe sequelae from cCMV occur in both maternal primary and non-primary infections [9].

Multiple studies show that non-primary CMV infections are not rare. For example, a recent study from Canada assessing reinfection, defined as the appearance of antibody response to a new epitope in the third trimester compared to the first trimester, reported reinfection rates comparable to primary infection [10]. Similar findings have been documented in studies from the United States [11] and Brazil [12].

Little is known about the potential impact of herd immunity, whether acquired through natural infection or vaccination, on CMV transmission dynamics within the human body. Reinfections can and do occur, but the extent to which preexisting immunity protects against reinfection is unclear. It is also uncertain whether the substantial genetic diversity among CMV strains plays a role in limiting the ability of preexisting immunity to provide protection from reinfections [13].

Although a correlate of protection to prevent CMV infection or congenital CMV infection has yet to be defined, a vaccine that induces immune responses of quality and magnitude similar to natural CMV infection could potentially reduce the rate of congenital CMV infection [14].

A recently conducted, Sponsor supported, phase 2b randomized placebo-controlled trial of V160 (V160-002), a whole-virus CMV vaccine candidate, assessed vaccine

efficacy against primary CMV infection among seronegative women aged 16 to 35 years [15]. As no validated serologic assay existed at the time of the trial to distinguish vaccine-induced from wild-type infection-induced antibodies, CMV infection endpoints in that study were defined virologically via PCR detection of CMV DNA in saliva and urine. Longitudinal sampling allowed characterization of shedding dynamics and immune responses. In the trial, a per-protocol case of primary CMV infection was defined as detection of non-vaccine CMV DNA based on PCR positivity in saliva or urine at any timepoint above the assay limits of detection (LOD). Across vaccination groups, fewer CMV infection cases were detected via urine than via saliva. Several per-protocol CMV infection cases did not develop neutralizing antibodies and had only a single time point of low-level shedding. This low-level virus detection may represent transient presence or aborted infections, consistent with reports that low-level shedding can occur without establishment of clinically-meaningful infection [16];[17].

Post-hoc analyses of V160-002 proposed that a refined case definition for primary CMV infection could be used to capture more accurately the true vaccine efficacy: wild-type DNA load of >450 IU/mL (239 copies/mL) in saliva and wild-type DNA detected in urine (above LOD) at the same timepoint. This refined definition markedly increased specificity and positive predictive value compared with the original protocol definition and greatly reduced false-positive cases that otherwise bias efficacy estimates toward the null [18].

To date, few studies have investigated CMV shedding in multiple specimen types following the primary infection of healthy adolescents or adults [14];[19]. As such, the dynamics of CMV shedding remain poorly understood [20].

Rationale

To reduce the burden of congenital CMV, associated with substantial long-term morbidity, CCI [redacted]. Primary and non-primary CMV infection in adults is typically asymptomatic or mild and lacks specific clinical symptoms. Vaccine trials require highly specific molecular or serologic case definitions to identify primary infections accurately. A CCI [redacted]

This study is designed to collect longitudinal saliva, urine, and blood samples from parents or caregivers of children attending day-care centers in France, as well as saliva and urine samples from their children. This setting is well-established as a high-risk environment for CMV transmission: children in day-care shed CMV at high prevalence, especially between 6 and 24 months of age, and parental infection is strongly associated with exposure to shedding infants [21]. Prior studies, including more than 90 day-care centers in France, reported CMV shedding prevalences of ~30 to 50% in young children [22], [23].

Early results from first trimester screening during pregnancy, recently implemented in France, indicate that, nationwide, approximately 48% of screened women are CMV-seronegative and therefore susceptible to CMV (unpublished data).

Data generated from this study will support CCI [redacted]

- Assessing the performance of PCR-based case definition criteria for identifying primary CMV infection

CCI [redacted]

- Describing viral and immune dynamics before, during, and after primary CMV infection

In addition, the study will update our knowledge of the Natural History of CMV infections in day-care centers using updated diagnostic tools based on composite endpoints.

5 RESEARCH QUESTION AND OBJECTIVES

All objectives for this study are descriptive or exploratory; therefore, no formal hypotheses will be tested.

The study will be conducted in two phases: a pilot phase and a main phase.

The pilot phase is expected to begin in September 2026 and will be conducted in two or three day-care centers. It is intended to mirror the design and procedures of the main phase and may be used to refine recruitment approaches, logistics, sample collection procedures, and questionnaire content. The main phase is expected to begin in September 2027.

Objectives of the pilot phase:

1. To assess participant compliance, including feasibility and acceptability of study procedures, and considering feedback from participants.

2. To evaluate the feasibility of the sample collection process, including:

    - Blood sampling in adults in local laboratories

    - Saliva and urine sampling in adults in local laboratories and via self-sampling at home

    - Saliva sampling in children in day-care centers

- Urine collection in children in day care centers using urine collection bags and/or from diapers (with a separate collection device insert)

3. To assess logistics related to local sample preparation, shipment, and storage.

4. To assess urine and saliva sample collection quality (since some samples will be self-collected), including human β-globin gene detection as an indicator of adequate specimen integrity.

5. To assess the clarity and completeness of the questionnaire, based on participant responses and assess acceptability of electronic questionnaires.

6. To assess participants' adherence to saliva and urine self-sampling and their preferred sample collection method (at local lab or at home by self-sampling).

Data from the pilot phase will not be analyzed separately for the primary or secondary objectives; pending feasibility confirmation and absence of material changes, data from the pilot phase will be pooled with data from the main phase per the Statistical Analysis Plan (SAP).

The pilot phase objectives will be presented whenever possible as descriptive statistics (e.g. compliance rates and sample adequacy criteria) in the pilot phase report. This data will inform procedural refinements, if needed, for the main phase.

Objectives of the main phase:

5.1 Primary Objective

Objective 1: To assess the performance of PCR-based case definition criteria for identifying primary CMV infection in parents/caregivers who are CMV-seronegative at baseline.

5.2 Secondary Objectives

Objective 2: CCI [redacted]

Objective 3: To estimate the incidence of primary CMV infection, defined as seroconversion among parents/caregivers who are CMV-seronegative at baseline demonstrated within the serology assays used in this study.

Objective 4: To estimate the incidence of non-primary CMV infection (see definition on page 8) among parents/caregivers who are CMV-seropositive at baseline.

Objective 5: To describe transmission patterns between children and their parents/caregivers.

5.3 Exploratory Objectives

Objective 6: To describe viral and immune dynamics before, during, and after primary CMV infection, using longitudinal sampling.

Objective 7: Among non-primary CMV infections, to distinguish reinfection (new strain) from reactivation (latent strain), using genotyping and serologic data.

6 RESEARCH METHODS

6.1 Study Design

This is a prospective, longitudinal cohort study in which participants are enrolled through day-care centers (DCCs) in France. The study will include two sequential phases: a pilot phase and a main phase. Both phases will use the same overarching design, sample collection schedule, and recruitment framework.

Pilot phase

The pilot phase aims to be initiated in September 2026 and will be conducted in two or three DCCs. A total of ~30 adults and ~15 children are expected to be enrolled and followed until August 2027. Its purpose is to evaluate feasibility and refine operational aspects of the main phase. Specifically, the pilot phase will mimic the main phase in terms of procedures, visit schedules, specimen collection, and questionnaires (see section 5 for detailed study objectives of the pilot phase).

If changes to study procedures are required based on lessons learned during the pilot phase, a protocol amendment will be implemented before initiation of the main phase.

Main phase

The main phase is expected to begin in September 2027 and will involve approximately 60 to 100 DCCs across France. Two cohorts will be enrolled and followed for one year each (cohort 1 from September 2027 to August 2028 and cohort 2 from September 2028 to August 2029).

Study site selection

Study site selection will be done in collaboration between the Principal Investigators, the Clinical Investigation Center (CIC) and the CRO.

Recruitment strategy

Study participants will be recruited through day-care centers. Investigators' experience will be leveraged to identify and implement best practices to maximize recruitment and retention.

Optimal study sites are large day-care centers, which are located near participating local laboratories, with (1) an expected high number of new day care attendees (who started day-care not earlier than 3 months before study enrollment) and (2) an expected low CMV seroprevalence rate among the parent/caregiver population.

Study initiation

Study initiation will be conducted using the same process as the previous day-care study [23].

The day-care director and, if applicable, the mayor of the city (for public day-care centers) will be informed about the study. Their approval is required to launch the study.

Enrollment will target parents/caregivers of children who are newly attending participating DCCs. Recruitment will take place during an information session for eligible parents/caregivers, organized by the daycare center director in collaboration with the doctor (pediatrician or general practitioner) in charge of the daycare center,

Principal Investigator or CIC staff. Parents/caregivers can also reach out to investigators or CIC staff over the hotline at any time in case they have any questions on the study.

At the end of the information session at the day-care, parents/caregivers will receive the Participant Information sheet and Informed Consent Form as hard copy or in an electronic format.

After the information session, the parents/caregivers have sufficient reflection time during which consent can be given at any moment. Depending on parents/care-givers preference, several scenarios are possible (see flow-chart: situation #1):

1. Parents/caregivers are choosing the hard copy:

    a. If the parent/caregiver decides to sign immediately after the information meeting at the day-care; the document is signed by the investigator in presence of the parent/caregiver.

    b. If the parents/caregiver decides to sign at a later date; he returns the document to the investigator using a prepaid envelope and providing his personal email address. The document will be returned by email to the participant after having been signed by the investigator.

2. Parents/caregivers are choosing the e-consent accessible via a secure platform on their computer, tablet or smartphone:

    a. The parent/caregiver provides electronic signature; the study investigator will sign the document electronically in turn.

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For parents/caregivers who did not attend the meeting at the day-care, a video-conference will be organized. After the videoconference, the parents/caregivers have sufficient reflection time during which consent can be given at any moment. They can also reach out to investigators or CIC staff over the hotline at any time in case they have any questions on the study. Depending on parent's/care-giver's preference, there will also be different scenarios (see flow-chart: situation #2):

1. Parents/caregivers are choosing the hard copy:

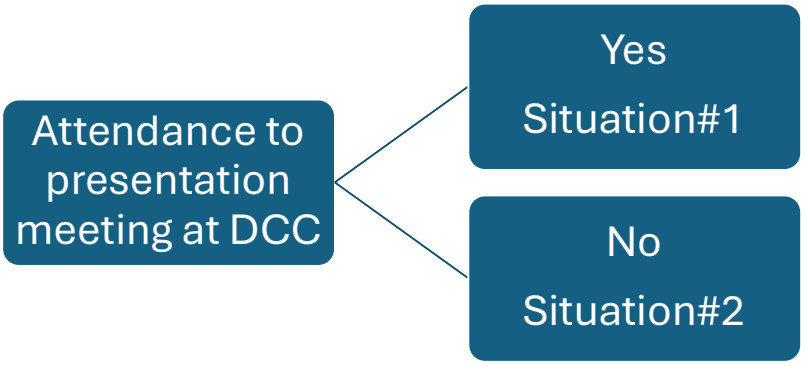
    a. The parent/caregiver picks up a hard copy at the day-care and returns the signed document to the investigator using a prepaid envelope and

providing his personal email address. The document will be returned by email to the participant after having been signed by the investigator.

2. Parents/caregivers are choosing the e-consent accessible via a secure platform on their computer, tablet or smartphone:

    a. The parent/caregiver provides electronic signature; the study investigator will then be invited to sign electronically in turn.

Figure A: Flow chart describing different scenarios of ICF signature



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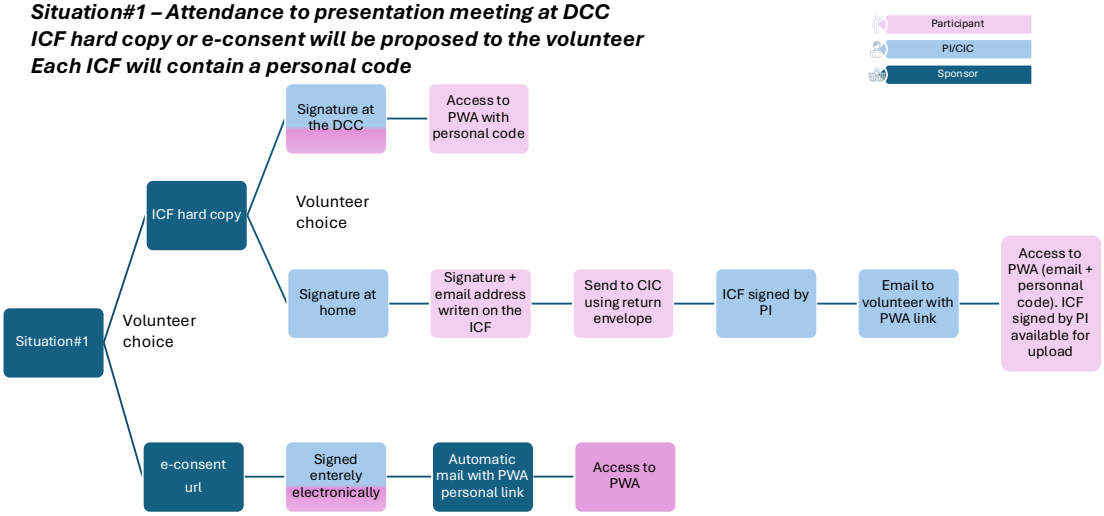
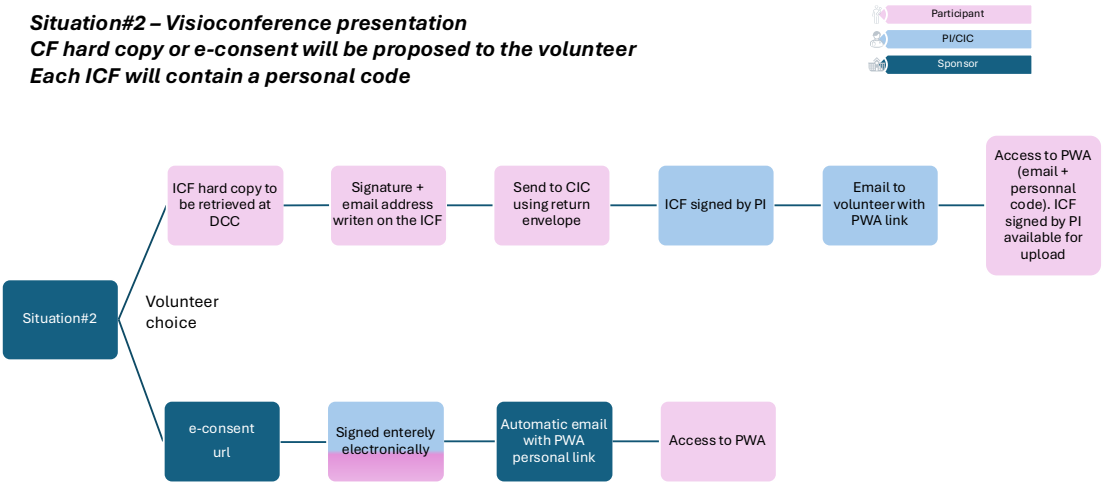
Situation#1 – Attendance to presentation meeting at DCC
ICF hard copy or e-consent will be proposed to the volunteer
Each ICF will contain a personal code



Situation#2 – Visioconference presentation
CF hard copy or e-consent will be proposed to the volunteer
Each ICF will contain a personal code



Whatever the scenario used, the informed consent contains a unique identification number that will be used during the participation in the study. Once the consent form is signed by the participant and the investigator, the participants will be invited to complete the questionnaire (see annex 1), available on the web platform.

Following completion of the questionnaire which will confirm eligibility, the platform will issue a unique Participant Trial Identification (PTID). This PTID serves as the

sole identifier for all participant-related data entries and for labeling biological samples across the study (See section 6.5.2).

Eligible adults will then be offered the option to include their child(ren)in the study. Children can only participate if they are attending one of the participating day-care centers, if at least one parent or caregiver is enrolled and if both parents sign the informed consent for the child (if both parents are living and have custodial rights).

Sample collection

After enrollment, all adult participants will attend a participating local laboratory for blood collection to determine CMV serostatus at baseline. Saliva and urine samples will also be collected during this first visit. Subsequently:

- Independent of CMV-serostatus at baseline, all adults will undergo saliva and urine sampling every month and blood sampling every 3 months. During the month, when only saliva and urine sampling is required, these can be collected through self-sampling at the participants' homes.

- Children will undergo saliva and urine* sampling every month at the DCC, at the same dates (+/- 7 days) as the sampling dates of their parents/caregivers, collected by day-care or laboratory staff onsite.

  *Viral shedding dynamics (timing after infection, viral load, etc.) have been shown to be varied in saliva versus urine. CMV generally has higher viral loads and occurs earlier post-infection in saliva, however, can occasionally yield false positives, i.e. when CMV is shed in maternal breast milk shortly after feeding. Urine generally contains large amounts of virus and has been considered highly reliable for confirming true infection. Both samples are needed to determine the best indicator of real infections and viral loads in transmission patterns.

Follow-up

Participants will be followed for 12 months.

- Adults who are CMV-seronegative at baseline will be followed to identify primary CMV infections. Participants who seroconvert during the study period will be further followed until the end of the follow-up period (ideally up to six months after seroconversion if feasible) to assess the dynamics and durability of immune response.

- Adults who are CMV-seropositive at baseline will be followed to identify non-primary CMV infections (reinfection with a different strain, or reactivation of latent CMV).

- Children will be followed for monthly CMV shedding, a key exposure measure for parental infection.

A new cohort of adults and children will be enrolled in the second year of the main phase. Based on data from the first year, enrollment targets and site selection may be adapted (e.g., replacing sites with high adult seroprevalence or low follow-up rates) to ensure the primary objective can be met.

Specimen collection and processing

All specimens will be collected according to standardized procedures described in the Laboratory Manual. Samples will be processed locally and shipped to designated testing laboratories (Sponsor's specialty laboratories and National Reference Center, as applicable). Aliquots of all samples will be stored locally during the study.

6.2 Setting *(study population and selection criteria)*

This study will include parents/caregivers of children attending participating DCCs in France, as well as their children who are attending the DCC. The primary setting for the study is DCCs located within the catchment areas of participating local laboratories to ensure feasibility of longitudinal sample collection.

Selection of day-care centers

DCCs will be selected in collaboration with the Principal Investigators, the Clinical Investigation Center (CIC), and the CRO. Selection will prioritize centers that:

- Are located within the operational catchment area of local laboratories supporting sample collection
- Serve populations with expected lower CMV seroprevalence among adults, (based on data available at day-care level to exclude day-cares from low socioeconomic environments where CMV seroprevalence is expected to be high among adults)
- Have sufficient CMV virus circulation/shedding among children (based on observations from CrechMV study [23])
- Serve a population with well-balanced CMV serology profile (~50% of CMV negatives) based on anonymous data from CMV national screening in the associated local laboratory
- Have a large number of enrolled children
- Are expected to have a high influx of new children at the start of each study year

Up to 3 centers will participate in the pilot phase, and approximately 60–100 centers will be included in the main phase.

Adult population

All parents (mothers and/or fathers) and caregivers (for definition see section 6.2.1) of children newly enrolled to one of the participating DCCs are eligible to participate in the study if they fulfill the inclusion criteria. For single-parent families or if only one of the parents/caregivers agrees to participate in the study, it is possible to include only one of the child's parents (mothers and/or fathers) or caregivers. Participation is voluntary and contingent on provision of informed consent.

Approximately 30 parents/caregivers are expected to be enrolled in the pilot phase. A total of approximately 2,000 parents/caregivers will be enrolled into the main phase across two study years (~1,000 at the start of Year 1 and ~1,000 at the start of Year 2), with the aim of achieving approximately 50% CMV-seronegative and 50% CMV-seropositive adults at baseline.

Child population

Children in France are generally eligible to attend DCCs from 3 months to ~3 years of age, with some remaining up to almost 4 years depending on school entry. All children with at least one parent/caregiver participating in this study are eligible for enrollment if they fulfill the inclusion criteria.

Approximately 15 children are expected to be enrolled in the pilot phase. A total of approximately 1,000 children will be enrolled in the main phase (about 500 in each study year).

6.2.1 Inclusion and Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

Inclusion Criteria

Adult population

- Parent or caregiver* of at least one child who recently (≤3 months before enrollment) started attending a participating DCC and who did not previously attend any other DCC.

- Aged 18 to 49 years at the time of informed consent.

- Able to understand study information in the informed consent and complete the questionnaire in French.
- Affiliated with a social security system or a beneficiary of such a system, unless an exemption applies.
- Provides written informed consent.
- Parent/caregiver of a child expected to remain in the DCC for the school year period (as declared by the parents).

  * Caregivers in this study refers to adults who provide regular care to the child, i.e., in the case of blended families, the partner of the mother or father of the child who lives in the same household with the child for at least 10 days a month.

Child population

- They recently started attending one of the participating day-care centers (≤3 months before enrollment in the study).
- At least one parent or caregiver is enrolled in the study.
- Both parents (if they are living and have custodial rights) provide written informed consent for child participation.

Exclusion criteria

Adult population

- Prior receipt of an experimental CMV vaccine.
- Parent of a child with known congenital CMV infection and/or disease.

Child population

- Parent(s) or caregiver(s) do not participate in the study.
- Known congenital CMV infection and/or disease (parent/caregiver-reported).

6.3 Variables

6.3.1 Outcomes

If any health outcomes are herein described, collected per the protocol, they will be summarized as part of any interim analysis (if required) and in the final study report in addition to being reported in real-time as individual AE/s if the criteria in section 8 are met. Refer to section 8 for AE reporting requirements and procedures.

This study includes the following outcomes of interest:

(1) CMV serostatus at baseline (adults)
(2) Primary CMV infection (adults)
(3) Non-primary CMV infection (adults)
(4) CMV DNA detection in saliva (adults)
(5) CMV DNA detection in urine (adults)
(6) CMV DNA detection in saliva (children)
(7) CMV DNA detection in urine (children)
(8) CMV genotypes in serum (adults who are CMV-seropositive at baseline)

Outcome definitions:

(1) CMV serostatus at baseline (adults)

Serostatus will be determined using a CMV commercial IgG and/or IgM assay [redacted]

- CMV-negative at baseline:
  - IgG negative and IgM negative
- CMV-positive at baseline:
  - IgG positive and IgM positive, or
  - IgG positive and IgM negative, or
  - IgG negative and IgM positive, or*
  - IgG positive and IgM equivocal, or
  - IgG equivocal and IgM positive*

* If results are IgM positive and IgG negative/equivocal, the IgG test will be confirmed. Testing procedures are specified in the assay SOP.

(2) Primary CMV infection (adults)

Primary CMV infection is defined as seroconversion, i.e. appearance of CMV IgG and/or IgM antibodies, using a commercial serology assay or CCI [redacted] in parents/caregivers who were CMV-seronegative at baseline.

This definition identifies incident infections in the seronegative cohort.

(3) Non-primary CMV infection (adults)

Non-primary CMV infection is defined as reinfection with a different strain, or reactivation of latent CMV in parents/caregivers who were CMV-seropositive at baseline (for more information, see section 7.3.1.

Additional classification criteria (reinfection vs. reactivation) will be supported by serologic patterns, viral load dynamics, and CMV genotyping (see Exploratory Objective 7).

(4-7) CMV DNA detection in saliva and urine (adults and children)

CMV shedding is defined as:

- Detection of CMV DNA by PCR above the assay limit of detection (LOD)
- In saliva or urine samples
- In either adults or children

These outcomes characterize shedding prevalence, magnitude, and temporal patterns.

(8) CMV genotypes

CMV genotyping will be performed via sequencing or validated genotypic assays to:

- Characterize viral strains,
- Distinguish reinfection from reactivation, and
- Explore transmission patterns.

A detailed genotyping workflow will be described in the Laboratory Manual.

6.3.2 Covariates

Covariates will be collected through questionnaires and laboratory data and will be used to describe the study population and support statistical analyses. Specific covariates included in analytic models will be detailed in the Statistical Analysis Plan (SAP).

Sociodemographic covariates

- Age
  - Calculated as age at enrollment.
- Sex assigned at birth
- Country of birth
- Parity (mothers only)
- Socioeconomic status
  - Captured via education level, profession, and household income indicators (as per questionnaire).
- Household size
  - Number of people living in the home, including number and ages of children.
- General CMV knowledge
  - Awareness of CMV and source of information (e.g., healthcare professionals, internet, media).
- CMV history
  - Self-reporting of CMV-serology.
  - Information about CMV congenital infection for the child.

Biological covariates

- Viral covariates
  - CMV viral load in saliva and urine (quantitative PCR)
  - Presence/absence of CMV DNA in each specimen
  - Serostatus and antibody titers using commercial CCI [redacted]

Additional biological covariates may be included based on emerging data (e.g., detailed antibody profiles, genotypic markers).

6.4 Data Sources

All data will be collected prospectively. Outcomes will be generated through biospecimen testing using commercial CCI [redacted]. Sample quality will be assessed during the pilot phase to guarantee that sampling, storage, and shipment processes are appropriate. Covariates will be collected from participants'

questionnaires. During the pilot phase, answers to questions will be assessed for completeness and consistency.

6.5 Study Procedures

Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety.

6.5.1 Medical History

As infection with CMV is a leading cause of morbidity in immunosuppressed individuals, participants will self-report a history of immune-compromising conditions and use of immunosuppressant medications in the questionnaire.

6.5.2 Assignment of Screening Number

All consented participants will be given a unique pseudonymized participant identification (PTID) number that will be used to identify the subject participant for all procedures during and after screening. Each subject will be assigned only one PTID and PTIDs will not be re-used for different subjects. Children will be attributed numbers that are related to those of their parents/caregivers so that they can be linked.

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6.5.3 Study Diagram

Table 1: **Schedule of activities for parents/caregivers**

Study Period:	**First visit**	**Follow-up visits**										
Visit Number/ Title: Study month[c]	**1**	2	3	4	5	6	7	8	9	10	11	12
Study Window		+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Informed Consent	x											
Inclusion/Exclusion Criteria	x											
Medical History	x											
Questionnaire [a]	x											
Saliva sample [b]	x	x	x	x	x	x	x	x	x	x	x	x
Urine sample [b]	x	x	x	x	x	x	x	x	x	x	x	x
Blood sample [b]	x			x			x			x		x

a. Details of sociodemographic questionnaire are described in Section 6.3.2and Appendix 1
b. Details of biospecimen collection, use, and storage are described in Section 6.5.5.
c. The visit windows provided should be followed, however sampling performed out of these windows will still be considered for analysis.

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Table 2: Schedule **of activities for children**

Study Period:	**First visit**	**Follow-up visits**										
Visit Number/ Title: Study month[b]	1	2	3	4	5	6	7	8	9	10	11	12
Study Window		+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7	+/-7
Informed Consent	x											
Inclusion/Exclusion Criteria	x											
Medical History	x											
Saliva sample [a]	x	x	x	x	x	x	x	x	x	x	x	x
Urine sample [a]	x	x	x	x	x	x	x	x	x	x	x	x

a. Details of biospecimen collection, use, and storage are described in Section 6.5.5.
b. The visit windows provided should be followed, however sampling performed out of these windows will still be considered for analysis.

6.5.4 Screening

Parents/caregivers who are willing to participate and have signed the informed consent form and the questionnaire will be evaluated to determine if they fulfill the inclusion criteria. Eligible parents/caregivers will be assigned a PTID and invited to attend a local laboratory for blood, saliva and urine sampling.

Children from parents/caregivers who are eligible for study participation and whose parents/caregivers provided an informed consent for study participation (signed by both parents/caregivers) will also be evaluated to determine if they fulfill the inclusion criteria. From those who are eligible, saliva and urine samples will be taken by day care or laboratory <personnel in the DCC.

6.5.5 Laboratory Procedures

All adult study participants will attend a local laboratory for baseline sample collection to determine their CMV serostatus at baseline. For this, a blood sample will be taken, and immunoassays will be utilized to measure the presence of CMV IgM and/or IgG antibodies. Commercial assays [redacted] will be used. At the same visit, saliva and urine samples will be collected and tested for the presence of CMV DNA by PCR.

At the first visit at the local laboratory, adults will present their PTID upon arrival. This PTID will be used as the unique identifier for all their samples across the study.

Subsequently, adults will be invited to local laboratories every month for saliva and urine sampling and every 3 months an additional blood sample will be taken. Depending on the results of the quality assessment of self-collected samples in the pilot phase, adults may also collect their saliva and urine samples by self-sampling at home during the main phase.

Saliva and urine samples will also be collected from children at the day care centers at baseline and subsequently every month. All samples will be tested for the presence of CMV DNA by PCR.

All samples will be shipped to the Sponsor's specialty laboratories, where the testing procedures will be performed.

All serum samples collected at each timepoint will be aliquoted and stored to allow repeat or confirmatory serologic testing, including adjudication of equivocal or IgG/IgM-only results, assessment of seroconversion, and any additional analyses required to support endpoint classification. Details of confirmatory testing procedures will be pre-specified in the SAP.

In addition, samples will be analyzed at the French National Reference Center.

Details are described in the study-specific Specimen Collection Procedures Manual, which is included in a separate Laboratory Manual.

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Table 3: Specimens to be collected, volume of specimens, and purpose of specimen collection

Specimen type	Visit	Volume for testing and banking	Purpose	Assay(s) (if applicable)
Serum (adults)	First visit	2 tubes of 7 mL whole blood = 14 mL (7mL of serum)	Determine CMV serostatus at baseline	Commercial serology assay(s), and/or CCI [redacted]
Serum (adults)	Follow-up visits	4 tubes of 7 mL whole blood = 28 mL (14 mL of serum)	Among CMV-seronegatives at baseline, identify CMV primary infection Among CMV seropositives at baseline, identify CMV non-primary infection	Commercial serology assay, and/or CCI [redacted] Strain-specific serology assay, and/or CMV scan
Saliva (adults)	First visit and follow-up visits	1 mL saliva in 1 mL transport buffer 1 FLOQ Swabs in 2 mL UTM	Detect CMV shedding	qPCR

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		1 FLOQ Swabs in 2 mL eNAT		
Urine (adults)	First visit and follow-up visits	3 mL in 1 mL UTM 2 mL in 2 mL of UTM 2 mL in 2 mL of eNAT	Detect CMV shedding/viral load	qPCR
Saliva (children)	All visits	1 saliva sponge collection device in 1 mL transport buffer 1 FLOQ Swabs in 2 mL UTM 1 FLOQ Swabs in 2 mL eNAT	Detect CMV shedding/viral load	qPCR
Urine (children)	All visits	Inserts in diapers before feeding, then collected after feeding, transferred into syringe for liquid extraction and then transferred 1.8 mL of the	Detect CMV shedding/viral load	qPCR

		liquid in 1.2 mL UTM		

*Universal transport medium

6.5.6 Future Biomedical Research (Required for Studies Collecting DNA)

The following specimens are to be obtained as part of Future Biomedical Research:

All blood (including the subcomponents of plasma and serum), saliva and urine samples will be stored and may be used, as needed, for additional activities to support CMV research. These include but are not limited to the development of assays. Additional research involving specimens from this study will be pre-specified in future amendments to this study protocol or in separate study protocols.

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before any procedure related to the Future Biomedical Research study. This includes the use of leftover specimens. A copy of the consent will be given to the subject.

6.5.7 Visit Requirements

Adults

During the first visit, parents/caregivers will be screened for CMV serostatus. CMV-seronegative participants will be followed to detect primary CMV infections, whereas CMV-seropositive participants will be followed to detect secondary CMV infections. Independently of serostatus at baseline, the adult participants will undergo the same longitudinal follow-up (see table 1). All parent/caregiver visits must be planned to coincide with their children's visits (+/- 7 days).

At the first visit, participants who report being assigned female sex at birth will be asked if they are currently pregnant.

Children

Children will be sampled in the daycare by DCC staff according to the schedule in table 2.

6.5.8 Other Procedures

Participant reminders for non-completion of study activities will be developed with expert input and specified in an SOP. Study staff will actively monitor for potential non-completion of study activities and may follow up with participants via text, email, and/or phone call.

Results of CMV testing will not be provided in real time to the participants for the following reasons:

1. CMV infection is generally asymptomatic and does not need any clinical care.
2. Free of charge first-trimester CMV screening during pregnancy has been implemented in France since June 2025 for all pregnant women.
3. No real-time CMV testing is planned in this study, therefore results are not intended to replace or complete the first-trimester CMV-screening.
4. Results can be obtained by participants on request as soon as they are available. The Principal Investigators or the CIC will provide the results to participants in this case.
5. Most recent CMV-serostatus will be provided to all participants at the end of the study.

6.6 Study Size

The sample size was determined to ensure adequate precision for the primary objective, which is to evaluate the performance of PCR-based case definition criteria for identifying primary CMV infection among adults who are CMV-seronegative at baseline.

Primary analysis population

The primary analysis will include adults who are CMV-seronegative at baseline. The study aims to enroll 1,000 seronegative adults, split across:

- ~500 participants enrolled during Year 1,
- ~500 participants enrolled during Year 2.

Given an expected ~50% sero-negativity rate among parents of young children in France, a total of 2,000 adults must be included. Accounting for an anticipated 5% loss to follow-up, approximately 2,105 adults will be invited to screening.

Use of National first trimester pregnancy screening data (Year 2 only) may support balancing seronegative and seropositive enrollment to maintain the desired ~50/50 distribution.

Incidence assumptions

There are no published data on primary CMV incidence among parents of children attending day-care centers in France. Based on results from the placebo group of the V160-002 trial [15], conducted in a demographically similar population (mothers with at least one child <5 years of age), the expected annual incidence of primary CMV infection is:

- 2.5% (expected)
- 1.5 to 3.5% (plausible range)

This corresponds to approximately 25 cases (range 15 to 35) within a cohort of 1,000 seronegative participants followed for 12 months.

These estimates are consistent with a meta-analysis reporting a mean annual seroconversion rate of 2.3% (95% CI: 2.1 to 2.4%) among seronegative pregnant women, with substantially higher risk among parents of shedding children [24].

Precision of sensitivity and specificity estimates

The performance of the refined PCR-based case definition for primary CMV infection will be evaluated by comparing the decision rule (e.g., wild-type DNA load of >450 IU/mL in saliva and wild-type DNA detected in urine at the same timepoint) against a composite endpoint based on totality of data (i.e., seroconversion and virologic pattern).

Sample size calculations followed the methodology of Hajian-Tilaki [25] for diagnostic test accuracy studies, in which precision of sensitivity and specificity estimates is determined using logistic regression with a binary marker.

With 1,000 seronegative adults followed over 12 months:

Sensitivity

- Expected sensitivity: 79% (range 73 to 85%)
- Estimated margin of error: 10 to 15% at expected 2.5% incidence

- Sufficient number of true-positive cases (~25) to support estimation

Specificity

- Expected specificity: >99% (range 96 to 99.99%)
- Estimated margin of error: 1 to 2%
- High precision maintained across incidence scenarios (1.5 to 3.5%)

Figures illustrating the sensitivity and specificity calculations (Figure B and Figure C) demonstrate that the planned sample size of 2,000 adults (with 1,000 seronegative) provides adequate precision for both measures.

Adaptive considerations

After completion of Year 1 of the main phase, the study size may be reassessed if the observed incidence of primary CMV infection differs substantially from expectations. Adjustments may include:

- Increasing or reducing Year 2 enrollment
- Replacing DCCs with high seroprevalence or low follow-up rates

Any modifications will be implemented before Year 2 begins.

No power estimations were performed for secondary and exploratory objectives.

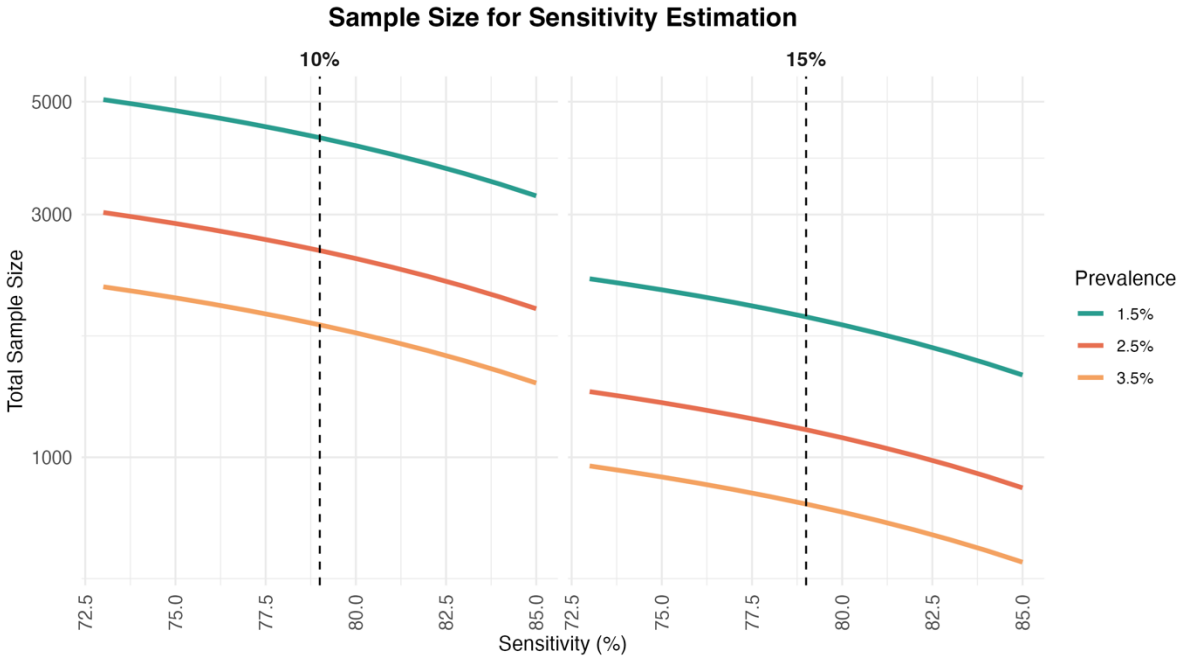

Figure B: Sample size requirements for sensitivity estimation of the PCR case definition for primary CMV infection. Total sample size is plotted against target sensitivity (%) for three prevalence levels (1.5%, 2.5%, 3.5%) at two margins of error (10%, 15%). Vertical dashed lines indicate the expected sensitivity of 79%.

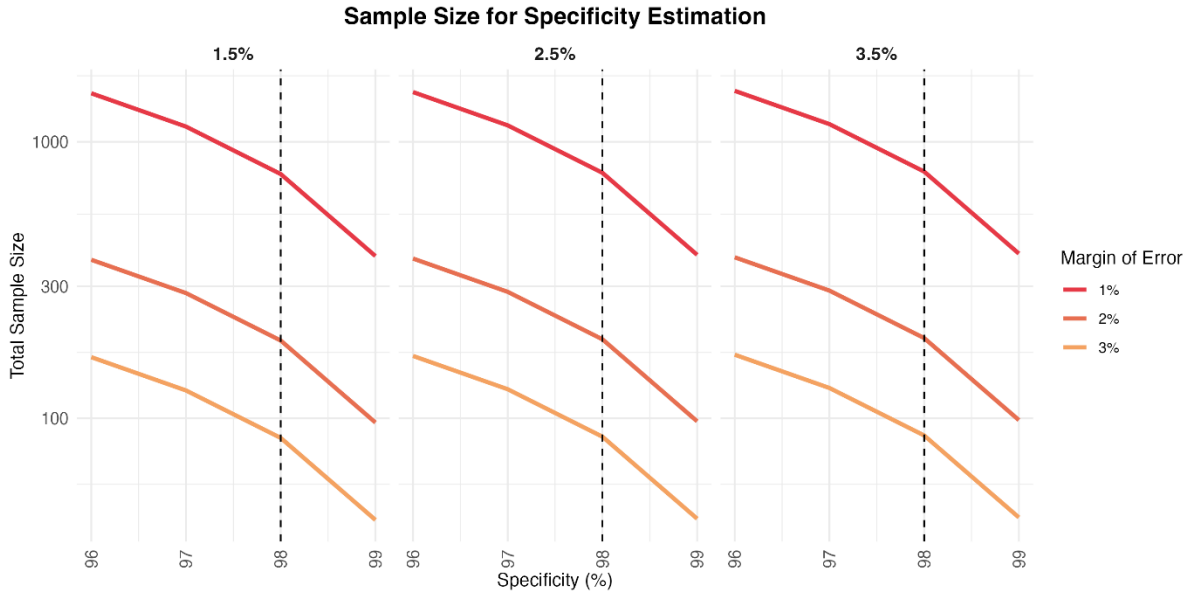

Figure C: Sample size requirements for specificity estimation of the PCR case definition for primary CMV infection. Total sample size is plotted against target specificity (%) across three incidence rates (1.5%, 2.5%, 3.5%) and three margins of error (1%, 2%, 3%). Vertical dashed lines indicate the reference specificity of 98%.

6.7 Data Management

All data collected for the study should be recorded accurately, promptly, and legibly. For primary data collection, the supplier and qualified designees are responsible for recording and verifying the accuracy of subject data. For data not obtained from a primary source (i.e., secondary data, such as claims and electronic health records), the investigator is responsible for reviewing data quality and relevance to the best of the investigator's knowledge. By signing this protocol either electronically or written, the investigator confirms that the quality and relevance of data has been assessed to meet the minimum requirements for all study objectives.

If this study has been outsourced, the institutional policies of the supplier should be followed for development of data management plans. However, the supplier should ensure compliance with Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

Specific details on data management procedures will be provided in the data management plan (DMP), which describes procedures related to data collection, handling, and review. The data will be collected using a database web platform

developed by ClinSearch, which will be used for the capture of questionnaires. The platform is compliant with the following standards:

- FDA CFR 21 part 11
- GAMP 5
- GCDMP
- Hosting, ISO 27001

Data will be recorded by participants through questionnaires. A questionnaire must be completed for each participant. The sociodemographic and health history questionnaire can be found in Appendix 1 and is described in Section 6.3.2.

In addition, sampling related data (e.g. date of sampling, sample quality…) will be recorded by the local laboratories in the database web platform.

Participants and local laboratories will attest to the authenticity of the collected data by reviewing and validating all data entries.

Ongoing data management and quality assurance tasks will include structural validation checks to limit errors upon data entry (e.g., consistency of date formats); automated reports to track the number of records completed and missing; resolution of duplicate records; and data review and tracking (including missing data, values within range, discrepancies).

Decisions on inconsistent or missing data remaining prior to analysis will be made at the data review meeting with the coordinating investigator and the sponsor.

Personal Data Protection

Data processing in the context of this study will be done in accordance with the European General Data Protection Regulation, called GDPR (EU 2016/679) and all applicable national laws on personal data protection.

The persons responsible for the quality control of data will take all necessary precautions to ensure the confidentiality of information relating to the study, the study participants and in particular their identity and the results obtained.

These persons are bound by professional secrecy.

During and after the research involving human participants, all data collected concerning the participants and sent to the sponsor will be rendered non-identifying.

All study reports will contain aggregate data only and will not identify individual participants.

Under no circumstances shall the names and addresses of the participants involved be shown.

In order to maintain patient confidentiality, each participant will be assigned a unique identifier upon study enrolment. This identifier will be used in place of the participant's name for the purpose of data analysis and reporting. All parties will ensure protection of participant personal data and will not include participant names or other identifiers (i.e. initials, full date of birth, address etc.) on any study forms, reports, publications or in any other disclosures, except where required by law.

6.8 Data Analysis

A detailed Statistical Analysis Plan (SAP) will be developed prior to database lock and will supersede this section where appropriate. The SAP will specify statistical methods, data derivations, handling of missing data, and planned sensitivity analyses.

6.8.1 Analysis Populations

Primary analysis population

Adults who are CMV-seronegative at baseline, followed for identification of primary CMV infection.

Secondary analysis populations

- Adults who are CMV-seropositive at baseline, followed for non-primary CMV infection.
- Children enrolled in the study, contributing data on CMV shedding as an exposure for parental infection.
- Parent/caregiver-child pairs with linked PTIDs.

6.8.2 Case Definitions Used for Analysis

Serology-based case definition for primary CMV infection

Primary infection to determine incidence rate in Year 1 and Year 2 will be defined as seroconversion using a commercial serology assay(s), i.e. appearance of CMV IgG and/or IgM antibodies CCI [redacted] in adults who are CMV-seronegative at baseline. (More details will be provided in the SAP).

PCR-based case definition for primary CMV infection

The refined PCR rule that will be evaluated: wild-type DNA load of >450 IU/mL in saliva and wild-type DNA detected in urine at the same timepoint in adults who are CMV-seronegative at baseline. Alternative PCR thresholds or rules may also be explored in sensitivity analyses.

Composite case definition for primary CMV infection

Totality of data on seroconversion by the commercial assay CCI [redacted] and longitudinal CMV viral shedding (i.e., wild-type DNA detected) in urine and saliva in adults who are CMV-seronegative at baseline. This definition serves as the comparator for evaluating PCR-based case definitions.

Non-primary CMV infection

The non-primary CMV infection is defined as CMV reinfection with a genetically distinct strain or reactivation of latent CMV in adults who are CMV-seropositive at baseline. Reinfection vs. reactivation will be further classified using:

- Genotypic data (if available),
- Antibody responses (commercial assay, strain specific serology assay CCI [redacted]
- Viral load patterns and shedding dynamics.

Non-primary CMV infection is defined as evidence of CMV reactivation or reinfection in adults who are CMV seropositive at baseline.

Primary operational criteria:

- New detection of CMV DNA by PCR above the limit of detection in saliva and/or urine in an adult who was CMV seropositive at baseline, particularly when confirmed across ≥2 consecutive samples and/or following a documented PCR negative period.

Supportive and classification criteria:

The following laboratory findings will be used to support classification and to distinguish reinfection from reactivation where feasible:

- Genotypic evidence of a CMV strain different from prior sequences from the same participant, consistent with reinfection
- Recurrence of the same CMV genotype following a documented PCR-negative period (defined as ≥2 consecutive scheduled saliva and urine

samples with CMV DNA below the assay limit of detection, occurring between PCR positive episodes), consistent with viral reactivation

- Significant rises in CMV-specific antibody titers (commercial[CCI] relative to prior measurements serving as supportive but not stand-alone evidence.

Genotypic analyses are contingent on PCR detectable CMV DNA and are therefore considered confirmatory rather than independent criteria.

Indeterminate findings:

Single, isolated low-level PCR-positive results without supportive serologic or genotypic evidence will be classified as indeterminate and will not be considered definitive non-primary CMV infections.

CMV detection in children

Children enrolled in the study will not undergo serologic testing, and therefore primary or non-primary CMV infection will not be defined for children. Instead, children will contribute PCR-based CMV shedding outcomes, defined as:

- Detection of wild-type CMV DNA above the assay limit of detection (LOD),
- In saliva and/or urine,
- At any scheduled sampling visit.

These shedding results will be used to:

- Characterize shedding prevalence and dynamics in the DCC population.
- Serve as a key exposure variable in analyses of child-to-parent CMV transmission.

6.8.3 General Analytical Principles

- All analyses will be descriptive or exploratory; no hypothesis testing is planned.
- Continuous variables will be summarized using mean, standard deviation, median, interquartile range, and range where appropriate.
- Categorical variables will be summarized using counts and percentages where appropriate.

- Time-to-event analyses will use Kaplan-Meier methods to estimate cumulative incidence where appropriate.
- Incidence rates will be calculated per 100 person-years, with 95% confidence intervals (CIs).
- Analyses will be stratified by variables of interest (e.g., sex, age, household size) where appropriate.
- All analyses will be conducted using validated statistical software.

6.8.4 Analyses by Objective

Objective 1: Evaluate PCR-based case definition for primary CMV infection

The refined PCR-based case definition will be compared against the composite serology-based and longitudinal viral shedding-based definition to estimate:

- Sensitivity
- Specificity
- Positive predictive value (PPV)
- Negative predictive value (NPV)

Exact 95% confidence intervals will be reported. Analyses will focus on the baseline-seronegative cohort of adults.

Analyses may include adjustments of both the refined endpoint and the composite rules definitions:

- Alternative saliva and/or urine PCR thresholds,
- Requirement for PCR positivity at multiple timepoints versus single timepoint,
- Incorporation of immune response magnitude or dynamics,
- Timing of PCR detection relative to seroconversion.
- Exploration of alternative (less frequent) sampling schedules by censoring data

Objective 2: CCI [redacted]

Analyses will include:

- Comparison CCI [redacted] with the commercial serology assays at months 1, 4, 7, 10 and 12 (see table 1).
- Among CMV-seronegative adults at baseline: agreement between CCI [redacted] and commercial assay-detected seroconversion.
- Among CMV-seropositive adults at baseline: durability and dynamics of antibody titers via observance of sustained or changing titer levels over time.
- Evaluation of assay performance, in terms of consensus CMV detection or reliability in determining CMVi, may incorporate the composite case definition as appropriate.

Cut-offs for CCI [redacted] will be evaluated.

- The current cut-off of the assay was set post-development and optimization and will be determined via a formal assay qualification process.
- The cut-off that is established during the assay qualification will be confirmed with this study population.

Objective 3: Incidence of primary CMV infection

Primary CMV infection is defined in Section 6.3.1.

Analyses will include:

- Cumulative incidence (Kaplan-Meier),
- Incidence rate per 100 person-years, with 95% CIs.

Person-time at risk will accrue from screening until seroconversion, loss to follow-up, or end of follow-up.

Objective 4: Incidence of non-primary CMV infection

Non-primary infection is defined in Section 6.3.1.

Analyses parallel those for primary infection:

- Cumulative incidence,
- Incidence rates per 100 person-years.

Reinfection versus reactivation will be explored descriptively (see Objective 7).

Objective 5: Transmission patterns between children and parents

Analyses will include:

- Association between child shedding (saliva/urine) at enrollment and parental serostatus.
- Among parents/caregivers who are seronegative at baseline: relative risk (or hazard ratio) of primary infection compared to those whose child sheds CMV vs. does not.
- Correlation analyses between:
    - Child viral load and parental seroconversion,
    - Duration of child shedding and likelihood of parental primary infection.

Exploratory modeling (e.g., Cox proportional hazards) may be included in the SAP.

Objective 6: Viral and immune dynamics around infection

Analyses will examine:

- Timing of first detectable shedding sample relative to seroconversion,
- Patterns and duration of shedding in saliva and urine,
- Antibody response trajectories (commercial CCI [redacted]),
- Earliest detectable indicators of infection.

Descriptive plots (e.g., spaghetti plots) may support interpretation.

Objective 7: Distinguishing reinfection versus reactivation

Among seropositive adults:

- Reinfection will be inferred from detection of new CMV genotypes over time.
- Reactivation will be inferred from recurrence of the same genotype with accompanying changes in viral load or serologic markers.

Analyses will be descriptive due to expected small numbers.

6.8.5 Handling of Missing Data

- Missing specimen results (e.g., skipped visits) will be summarized but not imputed.
- For incidence (of primary CMV infection) analyses, individuals will contribute person-time until the date of seroconversion, loss to follow-up, or end of follow-up.
- Sensitivity analyses may explore the impact of intermittent missing PCR values on classification of shedding duration.

6.9 Quality Control

By signing this protocol, all parties agree to following applicable standard operating procedures (SOPs). All parties also agree to ensuring all existing and new study personnel are appropriately trained to ensure the study is conducted and data are generated, documented, and reported in compliance with the protocol, Good Pharmacoepidemiology Practice (GPP), Good Pharmacovigilance Practices (GVP), and all applicable federal, state, and local laws, rules and regulations. All parties should maintain transparency and open communication in order to effectively manage the study and proactively mitigate any risks.

The Sponsor may conduct routine or for-cause audits to ensure oversight and conduct of the study are completed in accordance with the protocol, quality standards (e.g. GPP and GVP), and applicable laws and regulations. If a significant quality issue (SQI) is identified at any time during the conduct of the study, it must be escalated to the Sponsor immediately. A SQI is any issue with the potential to negatively impact, either directly or indirectly, the rights, safety and well-being of patients or study participants and/or the integrity of the data. In the event an audit or SQI results in corrective or preventive actions, all parties are expected to appropriately implement the action plan in a timely manner.

6.10 Limitations of the Research Methods

This study is subject to several limitations.

Given the longitudinal nature of this study, with monthly sampling, strong adherence from the study population and daycare staff is essential throughout the 12-month study period. This will be challenging, especially since the participants are parents of very young children, whose daily schedules are generally very busy. In France, obtaining a place in a daycare center is usually contingent on both parents working. Significant efforts will be made to encourage parents and daycare staff to participate in the study and adhere to the sampling schedule. These efforts will include direct communication from the principal investigators during information sessions at the

daycares, as well as reminders to participants who have not completed the scheduled activities. These reminders will be developed with the assistance of experts. In addition, when establishing the sampling schedule, particular attention will be paid to avoiding appointments during school holidays or periods when the daycares are closed. In addition, during the pilot phase, self-collection of saliva and urine samples in adults at their homes will be evaluated. If this method proves feasible, it will facilitate adherence to the sample collection schedule, as participants will only need to visit local laboratories every three months instead of every month when all samples need to be collected in the local laboratories. There is also a potential risk of loss of follow-up if parents move. This risk cannot be completely ruled out, but it will be limited because only parents who report that their child will remain in daycare for the entire school year will be included in the study.

The study setting and population have been specifically selected to increase the likelihood of detecting CMV infection cases. While the biology of CMV infection cases is not expected to be different between high-risk individuals and the general population, the incidence estimates of primary CMV infections observed in this study is estimated to be higher than in the general population.

7 PROTECTION OF HUMAN SUBJECTS

7.1 Informed Consent

This study will require written participant informed consent.

As described in section 6.1, all subjects will be provided with oral and written information describing the nature and duration of the study and the procedures to be performed. This document further explains the nature of the study, its objectives, and potential risks and benefits. Detailed information about potential expected side effects from Protocol Specified Procedure must be provided by the person in charge of subject information. It must clearly specify that the subject is free to withdraw from the study at any time without giving a reason.

The informed consent form and subject/child information sheet shall be written in the official language of the country where the study center is located and can be provided as hard copy or in an electronic format, depending on subject's preference. It should be non-technical and understandable.

The informed consent will adhere to IRB/EC requirements, applicable laws and regulations and Sponsor requirements. According to French law, the informed consent for children needs to be signed by both parents (if both parents are living and have custodial rights).

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/EC's approval/favorable opinion in advance of use. The subject should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form (hard copy or electronic format) along with the dated signature of the person conducting the consent discussion.

If a hard copy is used, a copy of the signed and dated consent form should be given to the subject before participation in the study. The original copy will be kept by the CIC.

In accordance with deliberation n ° 2026-050 of May 19th 2026, repealing Deliberation No. 2018-153 of May 3rd 2018, the sponsor has made a declaration of commitment to conformity with the relative methodology of reference relating to processing of personal data in the context of health research with the collection of the data subject's consent (MR 001), to the National Commission for Computing and

Liberties - (CNIL). The sponsor has ensured that this study is within the scope of the reference methodology MR-001.

7.1.1 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-study. A copy of the informed consent will be given to the subject. For specimens that are already collected (retrospective), please assess if re-consenting patients is required.

Future Biomedical Research (Required for Studies Collecting DNA)

The following specimens are to be obtained as part of Future Biomedical Research:

Blood for genomics use

Withdrawal From Future Biomedical Research (Required for Studies Collecting DNA)

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by writing to the principal investigator for the main phase. If medical records for the main phase are still available, the Investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the Investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research study data and results. No new analyses will be generated after the request is received.

In the event that the medical records for the main phase are no longer available (e.g., if the investigator is no longer required by regulatory agencies to retain the main phase records) or the specimens have been completely anonymized, there will no longer be a link between the subject’s personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

8 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Adverse Event (AE) and Product Quality Complaint (PQC) Reporting Language for Non-Interventional Study Protocols

Introduction

This is a primary data collection non-interventional study being conducted within routine medical practice. All direction for medication usage is at the discretion of a physician in accordance with usual medical practice. No administration of any therapeutic or prophylactic agent is required in this protocol.

8.1 Adverse Event and Product Quality Complaint Reporting

8.1.1 Investigator Responsibility

If adverse events (AEs) or product quality complaints (PQCs) are identified following use of any Sponsor product, then the AE* and/or PQC must be reported according to AE/PQC Reporting Table. If any health outcomes are described in section 6.3.1, they must be assessed for AE reportability according to the AE/PQC Reporting Table.

*For the purposes of this protocol, **the term "AE" collectively refers to the following reportable events** (refer to section 8.2 for definitions):

- Serious adverse events (SAEs), including death due to any cause
- Non-serious adverse reactions (NSARs)
- Special situations

AEs, PQCs, and AEs that occur in combination with PQCs, or spontaneously reported events, should all be captured using the AE/PQC report form for each patient and reported according to the AE/PQC Reporting Table.

The investigator must evaluate each SAE for causality and record causality on the report form for each SAE and NSAR reported

Protocol Specified Procedures: If the investigator becomes aware of an AE within 5 days of blood draw or within 2 days of saliva or urine sampling, they must evaluate, and report the AE per the *Supplier Protocol Specified Procedure (PSP) Adverse Events (AEs) Reporting Plan* and record it in the study database. Additionally, any AE brought to the attention of the investigator at any time after the above specified time period must also follow the *Supplier PSP AE Reporting Plan* and be recorded in the study database if it is felt to be causally related to the procedure. All subjects with SAEs related to protocol specified procedures must be followed up for outcome per the *Supplier PSP AE Reporting Plan* and all collected

SAEs for the procedure will be summarized in the final study report and any planned interim analysis.

AE/PQC Reporting Table: AE and PQC Reporting Timeframes and Process for Investigators/Suppliers

AEs AND PQCs	**INVESTIGATOR TIME FRAMES**	**SUPPLIER TIMEFRAMES**
	Investigator to Supplier [1]	**Supplier to Sponsor [2]**
SAE regardless of causality Serious Special Situation, regardless of causality	24 hours from receipt	1 BD/3 CD from time of receipt from investigator
NSAR Non-serious Special Situation, regardless of causality	10 CD from receipt	10 CD from time of receipt from investigator
PQC with or without an AE (SAE/NSAR/Special situation)	24 hours from receipt	24 hours from time of receipt from investigator
Follow-up to any AE/PQC-submit using above timeframes		
BD-Business Day; CD-Calendar Day		
Non-Sponsor Products: If the investigator elects to submit AEs/PQCs for **non-Sponsor products**, they should be reported to the market authorization holder (MAH) for that product or to the health authority according to the institution's policy or local laws and regulations.		
[1] Investigator to Supplier: AEs and PQCs for Sponsor products are submitted to Supplier via fax or secure email **[2] Supplier to Sponsor:** Supplier submits AEs and PQCs for Sponsor products to Sponsor for reporting to worldwide regulatory agencies as appropriate		
All AEs and PQCs must be submitted to Local DPOC via secure email: dpoc.france@msd.com, or using the platform for AE reporting: https://safetyreporting.msd.com/), or Local DPOC Mailbox Fax +33 1 80 46 40 41, in English using the AE/PQC reporting form.		

8.2 Definitions

8.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a

causal relationship with this product. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptoms, or disease temporally associated with the use of the product, whether or not considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product is also an adverse event.

8.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility.

8.2.3 Serious Adverse Event (SAE)/Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

8.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 8.2.3.

8.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Exposure to product during pregnancy or lactation
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent

- Unexpected Therapeutic Benefit/Effect

8.2.6 Product Quality Complaint (PQC)

Any communication that describes a potential defect related to the identity, strength, quality, purity or performance of a product identified by an external customer. This includes potential device or device component malfunctions.

8.2.7 Malfunction

The failure of a device (including the device component of a combination product) to meet its performance specifications or otherwise perform as intended. Performance specifications include all claims made in the labeling for the device.

8.2.8 Sponsor's product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

8.2.9 Causality Assessment

A causality assessment is the determination of whether or not there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

9 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The primary results of this research study will be externally disseminated in a manuscript submitted to a peer-reviewed, scientific journal, abstract/presentation at a scientific conference or symposium. Prior to external dissemination all sponsor publication requirements must be met, this includes but is not limited to completion of all authorship requirements. Any publication related to the study will need to be

reviewed/approved by the Sponsor prior to submitting results externally. Any publication resulting from this work will adhere to the procedures and pre-specified analysis plans within this protocol.

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PRODUCT: V16X	PROTOCOL/AMENDMENT **V2**
REV/OPS ID NO: NIS104141	NIR DRC APPROVAL DATE: 6/17/2026

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11SIGNATURES

11.1 Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other project plans and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and the Use and Disclosure of Personal Data notice provided to me, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

PRINTED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

11.2 Supplier

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); changes from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any adverse events and product quality complaints as defined in the Safety and Product Quality Complaint Reporting and Related Procedures section. I understand that information that identifies me will be used and disclosed as described in the protocol and in order to perform any agreement between myself and the Sponsor, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

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