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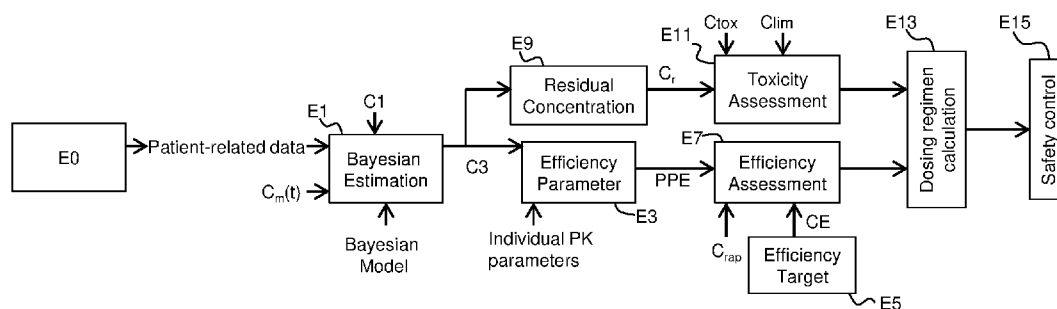


Fig. 4

(57) Abstract: The invention concerns a method determining an optimum drug dosing regimen to treat a patient efficiently against drug-sensitive pathogenic agents. From relevant patient-related data and the drug concentration measured at a random time in the patient's body, the method estimates the drug concentration time-course based on a Bayesian model. The residual concentration (C_r) and an efficiency pharmacokinetic parameter (PPE) adapted to said drug and patient are computed from the estimated concentration. A dosing regimen is then determined by comparing the PPE to an efficiency target (CE) for efficiency purposes. The method further may further take into account toxicity constraints by comparing the residual drug concentration (C_r) to at least a toxic concentration (C_{tox}). A concentration of said drug is determined (E13) based on the result the above comparisons to provide a proposed dose for said optimum dosing regimen.



METHOD FOR DETERMINING AN OPTIMAL DRUG DOSING REGIMEN

1. Field of the invention

The present invention concerns a method for determining drug dosing
5 regimens, in particular in case the drug is an anti-infective drug.

The invention is intended to assist a physician or a doctor in interpreting measured concentrations of a drug and in deciding on most appropriate doses of the drug to administer to a patient to be treated, while taking into account pharmacokinetic considerations and *concentration - effects* relationships.

10 The invention is particularly well-suited to provide an optimal drug dosing regimen that can be adapted individually to each patient, taking into account the characteristics of the patient, the characteristics of the drug used, the characteristics of the pathogenic agent (*e.g.* germ, bacteria or virus) found or suspected in the patient's body and the time at which the drug concentration was
15 measured in the patient's body.

The method according to the present invention contributes to optimize the treatment of a patient by determining the most appropriate dosing regimen (*e.g.* dose, dosing intervals and the infusion duration) that is adapted to the patient.

The invention may apply to any type of drugs or medicines that need to be
20 administered to a patient, such as anti-infective drugs to combat bacterial, fungal or viral infections.

2. Prior art

Even though the interpretation of biological tests may be facilitated by
25 existing standards, the interpretation of drug dosing still remains cumbersome, as it generally depends on the time elapsed between the time at which the drug was injected and the time at which its concentration was measured, as well as on the actual relationship between the drug concentration and its actual effects on the patient for the active molecule(s) of the drug at stake.

30 For many pharmacological laboratories or drug dosing platforms, it is common practice to provide antibiotics dosing results without any interpretation. In order to adapt dosage, the physician usually applies rules of thumbs, such as

rules of three based on time-constrained measurements of drug concentrations in the patient's body. Such a method is not only prone to errors but is also limited in terms of scope since interpretation may be provided only in very few specific cases.

5 For instance, the physician may interpret dosing results if the drug concentration is measured one or several days after starting the treatment and at a fixed time with regard to the time at which the drug was injected into the patient and if the efficiency target of the treating molecule is defined for a peak concentration or before the next drug injection.

10 In those specific cases, the interpretation performed by the physician consists in manually evaluating the current dosage but does not allow determining an optimal dosing regimen for the patient in order to optimize his/her treatment.

 For instance, if a concentration of amikacine is too high before injection, it
15 is advised to make another concentration measurement later (*i.e.* after injecting the dose into the patient's body). However, this method does not allow to estimate the reinjection time (*i.e.* time at which the next dose of drug should be injected).

 This represents a loss of opportunity for the patient who can seldom benefit from a drug dosing adaptation and even if such an adaptation is performed, it is
20 not optimal for the reasons as stated above. Under these conditions, it takes time for the patient to obtain efficient drug concentrations, which increases the risk for the patient to develop either resistance to anti-infectious treatments or toxicity issues.

 In order to overcome at least some of the above limitations and drawbacks,
25 mathematical tools exploiting Bayesian models have already been proposed to estimate, from the drug concentrations measured in the patient's body, the drug concentration time-course in the patient's body regardless of the drug treatment start time and the drug concentration measurement time with regard to the drug injection time and to simulate an optimal dosing regimen knowing the target drug
30 concentration to be reached.

 For instance, such solutions are implemented in existing softwares, such as *DoseMe*, *BestDose* or *Ezequiel*. However, using such softwares requires that

the user has performed a literature survey beforehand together with some pharmacological expertise in order to determine the target concentration. Besides, the user must simulate himself/herself the various dosage schemes or dosing regimens that may be used to reach the target concentration.

5 The paper entitled "Simulations of Valproate Doses Bases on an External Evaluation of Pediatric Population Pharmacokinetic Models" and published in *Journal of Clinical Pharmacology*, vol. 59, no. 3, March 2009, pages 407-417, Tauzin Manon *et al.* describes a method to determine doses recommendation in a population of children (not individual dose) of an antiepileptic drug to achieve
10 target concentrations through Bayesian estimation with the most appropriate population pharmacokinetic model.

WO 2017/180807 discloses a method and apparatus for providing a dosing regimen for a blood-clotting factor protein based on Bayesian estimations. For this protein, minimal FVIII activity concentrations should be greater than a
15 predetermined target trough concentration (1%) to minimize the risk for internal bleeding. In this document, the clinician may adjust manually the target.

Therefore, there is a need to evaluate the dose administered to the patient in terms of efficacy and toxicity and to determine quickly, automatically and with enhanced accuracy, optimal dosing regimens of a drug that a physician may
20 choose to administer to a patient in order to provide a treatment that is well adapted to the patient thereby overcoming the above-mentioned drawbacks.

3. Present invention

The present invention has been devised to address one or more of the
25 foregoing concerns.

According to a first aspect of the invention there is provided a method for determining an optimum drug dosing regimen to treat a patient efficiently against at least one drug-sensitive pathogenic agent.

This method comprises the following steps: obtaining patient-related data;
30 obtaining a concentration of said drug measured in the patient's body at an arbitrary time $C_m(t)$; from said measured concentration $C_m(t)$, computing an estimated drug concentration time-course by using a Bayesian model configured

according to an initial dose previously administered to the patient, mean values of parameters selected from said patient-related data and interindividual variability of said parameters .

For example, a biological parameter of a patient such as his/her weight or his/her renal function characterizing a medical condition (*e.g.* renal failure) may be used to configure the Bayesian model. The mean value and the variance with regard to the population of treated patients may be used for that purpose. By way of example, the variance or the standard variation may use to characterize interindividual variability amongst a population of patients.

More information on how to configure the Bayesian model may be found in the following article: Fuchs A., Csajka C., Thoma Y., Buclin T., Widmer N. - *Benchmarking therapeutic drug monitoring software : a review of available computer tools*, Clin. Pharmacokinet. 2013 January, 52(1) : 9-22.

The initial dose is a reference dose that has been previously administered to the patient, *e.g.* the latest administered dose. The value of the initial dose may have been determined by implementing the method according to the present invention. The value of this initial dose may be stored in a memory accessible by a software or application as described below.

The method further comprises the following steps :

- from said estimated drug concentration time-course, determining an efficiency pharmacokinetic parameter adapted to said drug and to said patient;
- a first comparison wherein said efficiency pharmacokinetic parameter PPE is compared to at least an efficiency target CE;
- a second comparison wherein a residual drug concentration C_r is obtained from said estimated drug concentration time-course and compared to at least a toxic concentration C_{tox} defined as a drug concentration beyond which serious side effects occur ;
- determining at least one concentration of said drug to treat said patient based on the result of said first and second comparisons to provide at least one proposed dose for said optimum dosing regimen.

According to another feature of the present invention, the efficiency target CE is defined as the product of a target ratio RC and a susceptibility factor SUS relative to said pathogenic agent, wherein:

- the target ratio RC is defined as the ratio to be reached to improve the drug efficiency based on known relationships between drug concentration and efficiency ;

- the susceptibility factor SUS is selected amongst the group of parameters including the minimal inhibiting concentration MIC, the inhibiting concentration that annihilates 90% (MIC_{90}) of the sensitive pathogenic agent, or the Epidemiological Cut Off Values ECOFF.

According to another feature of the present invention, the pathogenic agents are bacteria and the susceptibility factor (SUS) is set to be equal to:

- a maximum Epidemiological Cut-off Value (ECOFF_{max}) adapted to combat all bacteria that are usually sensitive and for which an ECOFF value is known or

- an ECOFF_{cut} for an empirical treatment adapted to combat most pathogenic agents excluding species having the highest ECOFF values according to known minimal inhibiting concentration distributions.

For instance, ECOFF_{max} and the ECOFF_{cut} values can be obtained from online databases.

According to another feature of the present invention, the efficiency pharmacokinetic parameter PPE is further compared to reported concentrations C_{rap} for said drug.

According to another feature of the present invention, the residual drug concentration C_r is compared to a limit concentration C_{lim} defined as the drug concentration for which an increased risk of side effects is reported.

According to another feature of the present invention, the efficiency pharmacokinetic parameter PPE is greater or equal to the efficiency target, the drug concentration is considered to be sufficient.

According to another feature of the present invention, if the efficiency pharmacokinetic parameter PPE is strictly less than the efficiency target CE, a

value of a percentage of drug-sensitive pathogenic agents which can be annihilated by the measured drug concentration is computed.

According to another feature of the present invention, the efficiency pharmacokinetic parameter PPE for an empirical treatment is strictly less than the efficiency target CE of certain sensitive strains of pathogenic agents, a value of a percentage of drug-sensitive pathogenic agents which can be annihilated by the measured drug concentration is computed for groups of suspected pathogenic agents.

According to another feature of the present invention, the patient-related data include the following parameters:

- the group consisting of biological characteristics such as age, gender, weight, creatinin clearance, and/or,
- the group consisting of previously administered dosage such as dose, time interval between two consecutive doses, infusion duration, reinjection time, and/or
- the group consisting of time delay between drug administration and measurement, measured drug concentration.

According to another feature of the present invention, a set of pharmacological safety rules is applied after determining said at least one dose of said drug.

Accordingly, the method according to the present invention may further comprise a control step subsequently to providing said at least one proposed dose, wherein :

- said proposed dose is increased by not more than 50% of said initial dose, except if the proposed dose is lower than a maximal dose recommended for said drug ; and/or
- said proposed dose is decreased by not more than 50% of said initial dose, except if the proposed dose is greater than said maximal recommended dose.

The control step is advantageous to adjust (*i.e.* increase or decrease) the proposed dose, in particular when very low or very high doses have been

previously administered to the patient, while keeping the proposed dose within safety limits (*i.e.* below the maximal recommended dose).

For instance, the maximal dose recommended for each drug used for treating the patients is obtained in product information or in guideline dosages for clinical practice published in the literature.

According to another feature of the present invention, the optimum dose regimen is obtained as a result of modifying the proposed dose first, then modifying a dose interval and finally modifying a duration of infusion for time-dependent antibiotics. For other categories of antibiotics (*i.e.* concentration dependent, time-and-concentration dependent), only the dose and the dose interval may be modified.

Another object of the present invention is a system comprising an application server and a client terminal, wherein the said client terminal or the application server is adapted to implement partly or fully the method as described above.

According to a feature of the present invention, the system further comprises a patient database from which the client terminal and/or the application server is adapted to retrieve patient-related data.

According to another feature of the present invention, the system further comprises a third-party database from which the client terminal and/or the application server is adapted to retrieve information on pathogenic agents and/or information on drug interactions.

At least parts of the method according to the invention as described above may be implemented by a computer or the like. Accordingly, the present invention may take the form of an entirely hardware embodiment, an entirely software embodiment (including firmware, resident software, micro-code, *etc*) or an embodiment combining both software and hardware aspects that may all generally be referred to herein as a "*circuit*", "*module*" or "*system*".

Furthermore, the present invention may take the form of a computer programme product embodied in any tangible medium of expression having computer usable programme code embodied in the medium.

Since the present invention can be implemented in software, the present invention can be embodied as computer readable code for provision to a programmable apparatus on any suitable carrier medium.

Thus, another object of the present invention is a computer programme comprising instructions adapted to implement any step of the method as described above when the programme is executed on a computer.

A tangible carrier medium may comprise a storage medium, such as a floppy disk, a CD-ROM, a hard disk drive, a magnetic tape device or a solid state memory device and the like. A transient carrier medium may include a signal such as an electrical signal, an electronic signal, an optical signal, an acoustic signal, a magnetic signal or an electromagnetic signal, *e.g.* a microwave or radiofrequency signal.

Thus, another object of the present invention is a medium for storing
5 information, removable or not, readable by a computer or a microprocessor and comprising code instructions of a computer programme adapted for implementing any step of the method as described above, when the programme is executed by a computer.

10 **4. Brief description of drawings**

The invention will now be described according to a particular embodiment of the present invention, by way of example only and with reference to the following drawings, in which:

- 15 - **Figure 1** illustrates schematically an example of a system wherein the present invention is implemented;
- **Figure 2** is schematic block diagram of a computing device for implementing the method according to the invention;
- **Figure 3** illustrates estimated drug concentrations over time;
- **Figure 4** illustrates the method of the invention according to a particular
20 embodiment; and
- **Figures 5 to 10** illustrates example decision trees for different cases of antibiotic data and bacteria data, for selecting a possible target.

5. Detailed description

Figure 1 illustrates schematically a system wherein the present invention may be implemented. For instance, the invention may be implemented in the context of a hospital where a physician or doctor 1 needs to decide on a dosing regimen of drug or medicine to be administered to a patient 2 infected by a pathogenic agent, such as a germ, bacteria or virus.

This system comprises a terminal 3 used by the doctor 1, an application server 4, a patient database 5 and third-party databases 6. The patient database 5 comprises information relating to patients who are being taken care of at the hospital.

The third-party databases 6 may comprise reference information relating to drugs (*e.g.* antibiotics) and pathogenic agents (*e.g.* bacteria). For instance, the third-party databases 6 may comprise one or more databases storing information on bacterial susceptibility, such as the one managed by the *European Committee on Antimicrobial Susceptibility Testing* (EUCAST), and/or databases storing information on drug interactions such as Micromedex.

The application server 4 is adapted to retrieve data from both databases 5, 6 via communication networks, such as the Internet (not illustrated). The application server 4 is also adapted to communicate with the terminal 3 via communication networks, such as the Internet and/or an intranet (not illustrated).

The system may further comprise a drug dosing device 7 adapted to measure the drug concentration in the patient's body (*e.g.* similarly to transdermal devices used to measure glycaemia in real-time). The drug dosing device 7 may comprise a wireless communication interface, so as to transmit and/or receive data to/from the terminal 3 via a local area network (not illustrated). The drug dosing device 7 may further be adapted to administer a dose of drug to the patient according to an instruction received from the terminal 3 operated by the doctor 1.

Figure 2 is a schematic block-diagram of the terminal 3 used for implementing one or more embodiments of the present invention. The terminal 3 may be a laptop, tablet, smartphone or the like adapted to store and execute a programme, software or application, wherein at least part of the method of the

present invention may be implemented. For example, the terminal 3 comprises a communication bus connected to:

- a central processing unit (CPU) 3.1, such as a microprocessor;
- a random access memory (RAM) 3.2 adapted to store the executable
5 code for implementing the method of the present invention, as well as registries adapted to save data, variables and parameters necessary for implementing the method according to one or more embodiments of the invention;
- a read only memory (ROM) 3.3 for storing computer programmes, softwares or applications in order to implement the embodiments of the present
10 invention;
- a network interface 3.4 connected to a communication network (intranet, extranet) through which medical data relating to patients, drugs, and/or bacteria may be received and/or transmitted. The network interface 3.4 may be a unique network interface or may comprise a set of different network interfaces (*e.g.* wired
15 or wireless). Data packets are sent through the network interface or received by the network interface under the control of the application, software or programme executed by the processor 3.4;
- a user interface 3.5 for receiving user inputs and/or displaying relevant information to the user (*e.g.* displaying one or more drug doses information to the
20 physician 1);
- an optional storage medium 3.6, such as a hard-drive or memory card (HD);
- an input/output 3.7 for receiving/sending data from/to external peripherals such as a hard-drive, removable storage media or the like.

25 The executable code may be stored in the read only memory 3.3, in the storage medium 3.6 or on a removable digital medium, such as a memory card.

Alternately, the executable code of the programme, software or application may be received in particular from the application server 4, by means of a communication network, through the network interface 3.4, so as to be stored in
30 one of the storage means of the terminal 3, such as the storage medium 3.6, before being executed.

The central processing unit 3.1 is adapted to command and manage the execution of instructions or code portions of the software, application or programme according to one of the embodiments of the invention, such instructions being stored in one of the above-mentioned storage means.

5 After start-up, the CPU 3.1 is able to execute instructions stored in the main RAM 3.2, with regard to the software, application or programme, after these instructions have been loaded into the ROM for instance.

Such a software, application or programme, when it is executed by the processor 3.1, implements at least some of the steps of the diagram shown in
10 figure 4.

In the preferred embodiment described herein, the terminal 3 is a programmable device that uses a software application configured to implement the method according to the present invention. As an alternative, the present invention may be implemented in hardware, for instance, in the form of a specific
15 integrated circuit or *Application Specific Integrated Circuit* (ASIC).

According to the present embodiment described in reference to figures 1 and 2 above, the programme configured to implement the method of the present invention is hosted and run by the terminal 3.

In alternative embodiments, this programme may be hosted and run by the
20 application server 4 or any remote server that has access to the patient database 5 and/or the third-party databases 6. In that case, the terminal 3 may be reduced to a lightweight client that is adapted to connect to the application server or the remote server via a communication network such as the Internet.

The present invention will now be described in the context of treating a
25 patient against a bacteria. However, the invention is not limited to this particular framework but can also apply to any other pathogenic agents such as viruses or fungi.

For treating a patient against a bacteria, the drug or medicine considered to treat the patient is an antibiotic. It is known that antibiotics may be classified in
30 three main categories or classes depending on whether their effect is time-dependent, concentration-dependent or concentration-and-time-dependent.

Time-dependent antibiotics (*e.g.* beta-lactams) are characterized in that the intensity of their activity on the bacteria is correlated with the duration during which the drug concentration in the patient's body exceeds a given threshold known as the *Minimum Inhibitory Concentration* (MIC).

- 5 Concentration-dependent antibiotics (*e.g.* aminosides) are characterized in that the intensity of their activity on the bacteria increases with drug concentration. Thus, a maximum or peak drug concentration must be reached in order to obtain an optimal effect on the bacteria.

- 10 Concentration-and-time-dependent antibiotics (*e.g.* fluoroquinolones) are characterized in that the intensity of their activity increases with the area under the drug concentration curve as a function of time. The area under the curve (AUC) is known as the exposure.

- 15 By default, the term *concentration* designates the total concentration of a drug in a patient's blood, which is the sum of the concentration of drug molecules in free form (*i.e.* unbound) and the concentration of drug molecules bound to the plasma proteins. This total concentration is either measured in the patient's body by sensors or estimated by means of mathematical tools.

- 20 Patient-related data may be inputted by the physician by means of the application through a human-machine interface displayed on the terminal 3. Alternatively, the patient-related data may be retrieved by the application from the patient database 5 via the application server 4 if this data is already stored in this database.

- 25 When launching the application, the physician is prompted to input, for instance through the human-machine interface by using the input/output interface 3.7, the patient's unique identifier to access his/her profile. Based on the information already available, the application may prompt the physician to complete and/or correct at least part of the patient-related data comprised within said profile.

- 30 Patient-related data may include at least one parameter selected from the group consisting of biological characteristics such as age, gender, weight, creatinin clearance or any covariable having an influence on the drug used to treat the patient. Covariable may include any treatment that may be used in

combination with the administration of said drug (*i.e.* co-treatment) and that may have an impact on the pharmacokinetics of said drug, for instance by interacting with said drug.

These parameters may be advantageously integrated in a pharmacokinetic model as described below. The patient-related data may also include the following parameters selected from:

- the group consisting of previously administered dosage such as dose, time interval between two consecutive doses, infusion duration, and/or
- the group consisting of time delay between drug administration and measurement, measured drug concentration.

The patient-related data may also include parameters from the group consisting of the identification of the pathogenic agent (e.g. bacteria, virus) and the identification of the minimum inhibitory concentration of the identified pathogenic agent.

Additional information may be added to the patient's profile, such as the infection location(s) in the patient's body.

Preferably, the application is adapted to prompt the physician to input only the data which are specific to the patient to be treated, *i.e.* patient-related data, while general information concerning antibiotics and bacteria or germs have been previously stored in the application. For that purpose, the application is adapted to update the general information from third-parties databases 6 by connecting to the application server 4 via its communication interface 3.4.

In an alternate embodiment wherein the application is executed directly on the application server 4, the application is adapted to send a data update request to the terminal 3, so that the user 1 can input patient-related data to be sent to the application server 4. This embodiment is particularly advantageous to strengthen patient's data privacy, in that his/her personal data are not stored directly on user terminal 3 but on a remote server that can be secured.

There exist population pharmacokinetic models of patients allowing to describe the concentration of a drug as a function of time for an average subject. A series of reference pharmacokinetic models may be stored on the application server 4.

These models may be accessible online and retrieved by the terminal 3 upon request or may be initially stored in a memory 3.3 (ROM) of the terminal upon installation of the application.

It is assumed that such a model (PopPK) is known for the active drug molecule used to treat the patient. According to the present embodiment, this model is stored in the ROM 3.3 of the terminal 3.

According to this pharmacokinetic model, the drug concentration expressed in mg/L on the Y-axis as a function of time in hours (h) on the X-axis is shown by the dotted curve C1 as illustrated schematically in **Figure 3**.

The application is configured to adapt this pharmacokinetic model by taking into account relevant patient-related data including biological information (*e.g.* age, weight, *etc*) and clinical data, medical condition or infection status (*e.g.* renal failure). For instance, if the patient is affected by renal failure, the pharmacokinetic model is adapted not only according to his/her weight but also according to his/her renal function, so as to obtain the corrected dashed curve C2 as shown in Figure 3.

It is assumed that the drug concentration is measured in the patient's blood at an arbitrary time t . A significant advantage of the method according to the invention is that it may be applied regardless of the time at which the drug concentration is measured in the patient's blood. It results therefrom that a drug dosing regimen may be determined with more flexibility, *e.g.* without having to observe specific times for taking measurements as conventionally required by existing dosing techniques.

The application advantageously obtains a measured value of the drug concentration, for instance from the measuring device 7 and adapts automatically the patient's pharmacokinetic model according to this measured value.

This measurement may be performed by the measuring device 7 itself which is coupled to the terminal 3. In that case, the application is advantageously configured to receive automatically at least one measured value for the drug concentration as depicted by $C_m(t)$ in Figure 3.

More precisely, the application is configured to estimate the drug concentration over time by applying a known Bayesian model based on said

measured value. This Bayesian model is advantageously configured so as to take into account inter-individual variability of parameters, for instance selected from patient-related data, as well as mean values of these parameters. This Bayesian model is preferably stored initially with the application on the terminal 3 or may
5 be stored in a memory of the application server 4 and/or retrieved upon request from the application server 4.

The result of this Bayesian estimation is shown in Figure 3 by the solid curve C3 that represents the estimated drug concentration over time. This curve C3 corresponds to a mathematical equation which depends on pharmacokinetic
10 parameters for absorption, distribution and/or elimination relating to the patient (*i.e.* individual pharmacokinetic parameters). These individual pharmacokinetic parameters are obtained by Bayesian estimation.

Referring to **figure 4**, main steps carried out by the application are illustrated.

15 At a step E0, the application obtains data.

More precisely, the obtained data first comprises the patient-related data related to the treated patient 2, for example inputted by the physician as explained previously.

In the described example, the obtained data further comprises drug data
20 relating to the drug used to treat the patient 2. In the described example, the drug is an antibiotic and the drug data includes an identification of the antibiotic and the category of the antibiotic, *i.e.* in the described example: concentration dependent, time dependant or time and concentration dependant.

Furthermore, in the described example where the drug is an antibiotic, the
25 obtained data comprises bacteria data identifying the bacteria or indicating that the bacteria is unknown. In the case that the bacteria is identified, the bacteria data further comprises the Minimum Inhibitory Concentration (MIC) of the identified bacteria or an indication that the MIC is unknown.

The obtained data may also comprises current dosing regimen data
30 related to the dosing regimen currently applied to the patient, in particular at least one amongst: its dose, its dose interval and its infusion duration.

The application is particularly advantageous in that it is adapted to compute a reliable estimation of the drug concentration automatically based on the pharmacokinetic profile expected for the patient, while taking into account his/her medical conditions (e.g. renal function) and a measured concentration
5 $C_m(t)$ in the patient's blood taken at an arbitrary time t . This computation is designated by step E1 in Figure 4.

If an applicable pharmacokinetic model exists, it can be applied to the patient, whatever the delay between drug administration and drug measurement is. In that case, the application is adapted to estimate a concentration interval
10 with a given prediction level that takes into account the uncertainty on said delay.

This interval is known as the *prediction interval*. For instance, with a prediction level set to 80%, the estimated concentration interval, also called the *80% prediction interval* on concentrations, is defined as the interval in which a future observation will fall, with a probability of 80%, given what has already been
15 observed. The prediction level may be set to other values, such as 85%, 90% or 95%.

One or more patient-related parameters may also be set with a prediction interval or uncertainty when configuring the Bayesian model by means of the patient-related data.

20 If no pharmacokinetic model is applicable to the active molecule of the drug or to the characteristics of the patient, the application may be configured to perform efficiency analysis and toxicity analysis according to paragraphs a) and b) below if the measured concentration (sample) is a residual concentration for time-dependent antibiotics and if peak and residual concentrations are measured
25 for concentration-dependent antibiotics.

For the remaining part of the description, it is assumed that a suitable pharmacokinetic model exists and is applicable.

a) Efficiency analysis

30 Based on the individual pharmacokinetic parameters derived from the above-described Bayesian estimation, the application calculates an efficiency pharmacokinetic parameter PPE, as depicted by step E3 in Figure 4. In general

terms, the efficiency pharmacokinetic parameter PPE is defined as the pharmacokinetic measurable quantity that is most appropriately linked to the efficiency of the acting molecule of the drug used to treat the patient. In other words, efficiency pharmacokinetic parameter PPE is a parameter of the estimated
5 drug concentration time-course C_3 (e.g. peak concentration, residual concentration or area under the curve).

According to the present embodiment, the application is configured to define the efficiency pharmacokinetic parameter PPE according to the category of antibiotics used to treat the patient and is further configured to calculate the
10 PPE value based on the results of the Bayesian estimation as previously obtained in step E1.

For time-dependent antibiotics, the application is configured to define the efficiency pharmacokinetic parameter as the total residual drug concentration C_r in the patient's body, just before next administration of the drug to the patient.

15 For concentration-dependent antibiotics, the application is configured to define the efficiency pharmacokinetic parameter PPE as the maximum or peak concentration C_{peak} .

For time-and-concentration-dependent antibiotics, the application is configured to define the efficiency pharmacokinetic parameter PPE as the
20 exposure which corresponds to the area under the curve AUC of the drug concentration. In that case, the value of the efficiency pharmacokinetic parameter is obtained by calculating the area between the estimated curve C_3 and the time axis (X-axis).

Once the efficiency pharmacokinetic parameter PPE is computed by
25 taking into account the antibiotic category in step E3 as described above, the application is adapted to compute an efficiency target CE as shown in step E5 to which the efficiency pharmacokinetic parameter PPE is then compared in step E7.

In step E5, the application is configured to define the efficiency target CE
30 as the product of a target ratio RC by a susceptibility factor SUS, *i.e.* $CE = RC \times SUS$. The target ratio RC is defined namely according to the antibiotics category as described below. In general terms, the value of RC may be

established from existing relationships linking drug concentration and efficiency as known in the literature which are prone to evolve as knowledge progresses. In that regard, the application may be configured to gather up-to-date data from the literature.

5 The susceptibility factor SUS represents the sensitivity of the bacteria to the antibiotics. The susceptibility factor SUS is defined in the application according to whether the bacteria has been identified or not, and if identified whether related parameters are known according to the different cases described below.

10 If the bacteria has been identified in the patient's body, the application is configured to set the susceptibility factor SUS as the *Minimum Inhibitory Concentration* (MIC) associated to the identified bacteria.

 If the bacteria has been identified but its inhibiting concentrations, *e.g.* MIC, are unknown, the application is configured to set the susceptibility factor
15 SUS equal to the *Epidemiological Cutt-off Value* (ECOFF) which corresponds to the highest minimal inhibiting concentration for any bacteria which has become sensible according to existing antibiograms. Such antibiograms may be obtained from the data retrieved in existing databases for instance managed by EUCAST. ECOFF values are determined from existing MIC distribution histograms as
20 available on the EUCAST online databases.

 If the bacteria has not been identified, the application is configured to apply a probabilistic treatment. In that case, the application is configured to define the susceptibility factor SUS as the maximum *Epidemiological Cut-off Value* (ECOFF_{max}) adapted to combat all bacteria that are usually sensitive and for
25 which an ECOFF value can be found in the EUCAST online databases.

 In specific cases, the application may be further configured to define the susceptibility factor SUS as a reduced *Epidemiological Cut-Off Value* (ECOFF_{cut}) that is adapted to combat most bacteria excluding species having the highest ECOFF values according to the MIC distributions as available on the EUCAST
30 online databases. In any case, the ECOFF_{cut} value is always lower than the ECOFF_{max} value.

For concentration-dependent antibiotics such as amikacine, gentamicine, the application is configured to set the susceptibility factor SUS equal to the inhibitory concentration adapted to annihilate 90% of the sensitive bacteria (MIC_{90}).

5 The application is configured to select the susceptibility factor from the parameters MIC, MIC_{90} , ECOFF, $ECOFF_{max}$, $ECOFF_{cut}$ as described above. This list of parameters proves to be sufficient to account for the vast majority of situations that a physician may encounter when treating patients. These parameters may be obtained from EUCAST online databases 6 and stored locally
10 on the terminal 3 or may be retrieved on-the-fly from the application server 4 to which the application is connected.

For instance, according to clinical practice, the specific efficiency target for the bacteria infecting the patient 2 is only known to the doctor when the MIC of the bacteria is known, e.g. free concentration is greater than four times the MIC
15 value for beta-lactams, or exposure is greater than 100 to 125 times the MIC value for fluoroquinolones. However, in case the MIC value is unknown, the prior art methods as described in the paper Simulations of Valproate Doses Bases on an External 5 Evaluation of Pediatric Population Pharmacokinetic Models or WO 2017/180807 do not provide any information on a target to be reached to
20 efficiently treat a patient. The present invention advantageously calculates an efficiency target in various cases, e.g. not only when the MIC is known, but also when the germ (or bacteria) is known but the MIC is unknown for this germ, or event when the germ is not identified.

In that regard, the calculation of the efficiency target according to step E5
25 is comprehensive and thus advantageously adaptive in that it provides a target to be reached so as to efficiently treat a patient in the vast majority of possible cases. It results therefrom that the method of the present invention greatly helps the doctor in determining an effective dose to administer to the patient in every situation.

30 In a first comparison step E7, the application is configured to compare the efficiency pharmacokinetic parameter PPE to the efficiency target $CE=RC \times SUS$.

For time-dependent antibiotics, PPE is set to the total residual concentration C_r that is either measured or estimated as described above in reference to Figures 3 and 4. In that case, the application is configured to compare this total residual concentration C_r with $CE = RCT \times SUS$, wherein RCT is an efficiency ratio that designates the total target ratio that the total residual concentration must reach to improve the efficiency of the active molecule of the drug. For instance, the application is configured to calculate the total target ratio $RCT = C_r / F$, wherein C_r is total residual concentration and F is the percentage of active molecules in free from (*i.e.* unbound).

For concentration-dependent antibiotics, PPE is set to the peak concentration C_{peak} that is either measured or estimated as described above in reference to Figures 3 and 4. The application is configured to compare the peak concentration C_{peak} with $CE = RCF \times SUS$, wherein RCF is an efficiency ratio that designates a fixed efficiency ratio. For instance, the application is adapted to calculate $RCF = PPE / MIC_{90}$. By way of example, for amikacine, CE is set between 60 and 80 mg/L, which corresponds to a RCF equal to 8 to 10 times and the SUS is the highest MIC_{90} value for the bacteria that are targeted.

For time-and-concentration dependent antibiotics, PPE is set to AUC that is calculated from the concentration curve C3 as described above in reference to Figure 3.

To sum up, the application is configured to compute the parameters as shown in Table 1 below and determine in the first comparison step E7 whether the condition $PPE \geq CE$ is verified.

Antibiotics Category	PPE	CE = RC × SUS	
Time-dependent	C_r	RC=RCT	SUS = MIC, ECOFF or ECOFF _{max} , ECOFF _{cut}
Concentration-dependent	C_{peak}	RC=RCF	SUS = MIC_{90}
Time & concentration-dependent	AUC	RC	SUS = MIC, ECOFF or ECOFF _{max} , ECOFF _{cut}

Table 1. Efficiency parameters computed by application

In general terms, if the $PPE \geq CE = RC \times SUS$, the drug concentration is considered to be satisfactory.

Otherwise, the application may be configured to determine and display on the terminal 3 relevant information that is valuable to the physician for administering a drug to the patient, such as an estimation of the percentage of bacteria that can be combatted by the measured drug concentration $C_m(t)$. Indeed, the physician may react differently in a situation where only 20% of the bacteria can be fought and in a situation where as much as 95% of the bacteria can be fought.

10 If $PPE < CE = RC \times SUS$, the application may be adapted to display:

- the value "*insufficient concentration or exposition (AUC)*" if the MIC of the bacteria is known;

- the value of a "*satisfactory concentration or exposition for a certain percentage of sensitive strains of the bacteria*", if the bacteria is known but its MIC is unknown;

- the value of a "*satisfactory concentration or exposition for a certain percentage of the sensitive strains of a first bacteria and another percentage of the sensitive strains of a second bacteria*" in case of probabilistic treatment.

In step E7, the efficiency pharmacokinetic parameter PPE or the efficiency target $CE = RC \times SUS$ may be compared to reference drug concentrations that are reported in the literature C_{rap} . Indeed, if the SUS is much lower than standard values (e.g. $CE < 10 \times C_{rap}$), the PPE will also be compared to reported concentrations in the literature, for time-dependent or time-and-concentration-dependent antibiotics. If the efficiency pharmacokinetic parameter PPE is much lower than reference drug concentration as reported in the literature (e.g. $PPE < 10 \times C_{rap}$), a dose adaptation could be proposed depending on the clinical context.

b) Toxicity Analysis

In step E9, the application determines the residual concentration C_r which is defined as the total concentration of a drug that remains in the patient's body just before the next administration of the drug. Step E9 may be automatically

executed in parallel to determining the efficiency parameter in step E3, as soon as Bayesian estimation is performed in step E1.

It is understood that this total residual concentration C_r is the sum of the concentration of drug molecules in free form (*i.e.* unbound) and the concentration of drug molecules bound to the plasma proteins. The total residual concentration is either measured in the patient's body by sensors (*e.g.* by means of a measuring device 7) or estimated by the application from the estimated concentration evolution computed in step E1 (*i.e.* corresponding to curve C3 as depicted on Figure 3).

In a second comparison step E11, the application compares the residual drug C_r concentration to the toxic concentration C_{tox} defined, as explained previously, as a drug concentration beyond which serious side effects occur. This comparison occurs only when the residual drug C_r concentration is higher than the reported concentrations C_{rap} .

In some cases, the application may be configured to further compare the residual drug concentration C_r to the limit concentration C_{lim} defined, as explained previously, as the drug concentration for which an increased risk of side effects is reported, for instance in online databases to which the application has access. This concentration may be overpassed, if it is considered that the benefits of the treatment are higher than its risks. The application is configured to perform this additional comparison, when the residual concentration is higher than reported concentrations and lower than the toxic concentration.

For time-dependent antibiotics, the application is configured to determine first whether the residual concentration C_r is greater than the toxic concentration C_{tox} (*i.e.* $C_r > C_{tox}$) and then whether the residual concentration C_r is greater than the limit concentration C_{lim} (*i.e.* $C_r > C_{lim}$).

For concentration-dependent antibiotics, the application is configured to determine whether the residual concentration C_r is greater than the toxic concentration C_{tox} . Limit concentrations are actually not determined for this class of antibiotics.

For time-and-concentration-dependent antibiotics, the application is configured to determine whether the residual concentration C_r is greater than the

limit concentration C_{lim} . The limit concentration may be replaced by the highest concentration reported in the literature without reported adverse events.

Based on the results of the first and second comparison steps E7, E11, the application is configured to generate and display a message on the terminal to provide appropriate recommendations or warnings to the physician 1. In particular, the application is configured to determine if the residual concentration C_r is greater than the limit concentration C_{lim} and/or if the residual concentration C_r is greater than the toxic concentration C_{tox} , *i.e.* $C_r > C_{lim}$ and/or $C_r > C_{tox}$ and the application is adapted to display this information.

For instance, the application may indicate whether the residual concentration is satisfactory, insufficient or toxic together with background information relating to the *concentration-effect* relationships which have been referred to for setting the limit and/or toxic concentrations.

c) Dose calculation

Based on the results of the first and second comparison steps E7, E11, the application is further configured to compute in step E13 a dosing regimen by calculating at least one of the following parameters: a dose, dose interval, an infusion duration. This calculation is performed by the application by taking into account the antibiotic category (*i.e.* time-dependent, concentration-dependent, time-and-concentration dependent).

The application is configured to run simulations by adjusting at least one of these three parameters and provide optimum dosing regimens.

For concentration-dependent antibiotics, the application is configured to determine the following parameters:

- a target dose, *i.e.* a dose to administer to the patient so that the peak concentration corresponds to the middle of the target interval (*e.g.* target being between 8 and 10 times the MIC_{90});

- a time interval between two consecutive doses ;

- a time for re-injection (*i.e.* for injecting another dose) defined as the time before the drug concentration becomes lower than a predetermined threshold (*e.g.* $C < 0.8 \times C_{tox}$).

For any other antibiotics, the application is adapted to calculate one or more of the following dosing regimens (*i.e.* dose, dose interval, infusion duration) which are adapted to reach the efficiency target while meeting the toxicity constraints as defined above:

- 5 - DoseMIC: defined as a dose, dose interval, infusion duration to administer so that $PPE/MIC=RC$;
- DoseECOFF: defined as a dose, dose interval, infusion duration to administer so that $PPE/ECOFF=RC$;
- DoseECOFF_{max}: defined as a dose, dose interval, infusion duration to
10 administer so that $PPE/ECOFF_{max}=RC$;
- DoseECOFF_{cut}: defined as a dose, dose interval, infusion duration to administer so that $PPE/ECOFF_{cut}=RC$;
- DoseRap: defined as a dose, dose interval, infusion duration to administer so that the residual concentration reaches reported concentrations
15 Crap;
- Doselim: defined as a dose, dose interval, infusion duration to administer so that the residual concentration is equal to the limit concentration C_{lim} ;
- Dosetox: defined as a dose, dose interval, infusion duration to administer so that the residual concentration reaches the toxic concentration C_{tox} but without
20 overrunning C_{tox} .

Dose calculations are made by the application using the equation of the concentration as a function of time, described in the literature, with the individual parameters calculated for the patient.

For example, when the dose interval and infusion duration are left
25 unchanged, the residual concentration Cr or area under the curve AUC stays proportional to the dose. Therefore, the calculated dose may be obtained from the initial dose, the Cr or AUC target and the measured Cr or AUC, for example by: $\text{calculated dose} = \text{initial dose} \times \text{Cr or AUC target} / \text{measured Cr or AUC}$.

A first dose and dosing interval modification are proposed by the
30 application. For instance, for time-dependent antibiotics, if this modification is not sufficient, an increase of the duration of infusion is proposed by the application.

Changing the infusion duration for time-dependent antibiotics in addition to adjusting the first dose and the dosing interval is particularly advantageous to reach the target concentration.

In particular embodiments, the application is adapted to propose several
5 doses. For illustration purposes, we consider the example of an empirical treatment supposing that the concentration is insufficient to fight against all the sensitive strains of the bacteria but already above the limit concentration. In that case, the application is adapted to propose a first dose equal to DoseECOFFmax to fight against 100% of the sensitive strains and a second dose equal to Doselim
10 to reach the highest concentration, thereby limiting toxicity risks. Thus, the application allows the clinician to adapt the dose as a function of the patient's clinical context, *e.g.* either increase the dose to DoseECOFFmax for lack of efficacy or decrease the dose to Doselim in case of adverse events.

Existing safety rules may be applied after calculating the doses to adjust
15 the proposed dose within safety limits. For that purpose, the application is adapted to apply safety rules in a control step E15 after providing the dose at the outcome of step E13. These safety rules may be predefined in the application and updated or retrieved from existing reference databases.

During the control step E15, the proposed dose may be increased or
20 decreased as a function of the initial dose and the recommended maximal dose. By default, the initial dose is defined in the application as the most recent dose that was administered to the patient. The history of all administered doses is stored by the application.

The application is adapted to read the value of the initial dose that was
25 stored in a memory of the application server or in the memory of the terminal from/on which the application is executed.

For instance, the proposed dose is increased by not more than 50% of said initial dose, except if the proposed dose is lower than the maximal recommended dose.

30 For instance, the proposed dose is decreased by not more than 50% of said initial dose, except if the proposed dose is greater than said maximal recommended dose.

For time-and-concentration dependent antibiotics, if the exposure is lower than CE, a DoseMIC, a DoseECOFF, a DoseECOFFmax or a DoseECOFFcut is determined, residual concentration produced is then compared to the limit concentration.

5 For all drugs, a maximum 50% increased dose will be proposed, except if this new dose remains under the maximal recommended dose. A maximum 50% decreased will be proposed except if the new dose remains greater than the maximal recommended dose or for important over-dosage.

10 From what precedes, it is apparent that the application determines (for example at step E5) possible target(s) to be reached by the treatment. For time dependant antibiotics and time and concentration antibiotics, the possible targets include at least one possible target for the efficiency pharmacokinetic parameter PPE and one possible target for the residual drug concentration Cr.

15 The possible target for the residual drug concentration Cr is the limit concentration Clim. The limit concentration Clim is evidently lower than the toxic concentration C_{tox}. This limit concentration Clim therefore represents an increased risk target for which an increased risk may occurs for the treated patient 2, but may be beneficial to the treated patient 2.

20 The possible target(s) for the efficiency pharmacokinetic parameter PPE may be determined from the obtained drug and, in the described example, also from the bacteria data (for example obtained at step E0). In the described example, the target(s) for the efficiency pharmacokinetic parameter PPE include at least one efficiency target CE as explained previously and, in some cases, the
25 reported concentration Crap. The reported concentration Crap is the concentration used in the literature independently of the bacteria. Evidently, the reported concentration Crap is always lower than the limit concentration Clim and the toxic concentration C_{tox}.

To sum up what was previously explained for the described example:

30 For a time dependant antibiotic with an identified bacteria and known MIC, the possible targets are: the efficiency target CE = RCTxMIC and the reported concentration Crap for the efficiency pharmacokinetic parameter PPE being the

residual concentration C_r and the limit concentration C_{lim} for the residual concentration C_r .

For a time dependant antibiotic with an identified bacteria and unknown MIC, the possible targets are: the efficiency target $CE = RCT \times ECOFF$ and the reported concentration C_{rap} for the efficiency pharmacokinetic parameter PPE being the residual concentration C_r and the limit concentration C_{lim} for the residual concentration C_r .

For a time dependant antibiotic with an unknown bacteria, the possible targets are: the efficiency target $CE = RCT \times ECOFF_{max}$, the efficiency target $CE = RCT \times ECOFF_{cut}$ and the reported concentration C_{rap} for the efficiency pharmacokinetic parameter PPE being the residual concentration C_r and the limit concentration C_{lim} for the residual concentration C_r .

For a time and concentration dependant antibiotic with an identified bacteria and known MIC, the possible targets are: the efficiency target $CE = RC \times MIC$ for the efficiency pharmacokinetic parameter PPE being the area under the curve AUC and the limit concentration C_{lim} for the residual concentration C_r .

For a time and concentration dependant antibiotic with an identified bacteria and unknown MIC, the possible targets are: the efficiency target $CE = RC \times ECOFF$ for the efficiency pharmacokinetic parameter PPE being the area under the curve AUC and the limit concentration C_{lim} for the residual concentration C_r .

For a time and concentration dependant antibiotic with an unknown bacteria, the possible targets are: the efficiency target $CE = RC \times ECOFF_{max}$ and the efficiency target $CE = RC \times ECOFF_{cut}$ for the efficiency pharmacokinetic parameter PPE being the area under the curve AUC and the limit concentration C_{lim} for the residual concentration C_r .

It is further apparent that the application may, at a first comparison step S1, compare the efficiency pharmacokinetic parameter PPE to at least one of the possible target(s) for the efficiency pharmacokinetic parameter PPE. For example, at step E7, the efficiency pharmacokinetic parameter PPE may be compared to the efficiency target CE. Furthermore, also at step E7, the efficiency

pharmacokinetic parameter PPE may be compared to the reported concentration C_{rap} .

It is further apparent that the application may, at a second comparison step S2 (for example corresponding to step E11), compare the residual drug
5 concentration C_r to the toxic concentration C_{tox} and to the limit concentration C_{lim} .

It is further apparent that the application may, at a third comparison step S3, compare to each other at least some of the possible targets. For example, at step E7, the efficiency target CE may be compared to the reported concentration C_{rap} .

10 It is further apparent that the application may select at least one (and preferably not all) of the possible targets according to the first and second comparison steps S1, S2, along with the third comparison step S3 in some cases.

It is further apparent that the application may determine, for each selected target, a dosing regimen to reach this target and display this dosing regimen. For
15 example, as explained previously, if the target $RC \times MIC$ is selected, the application may determine and display the DoseMIC dosing regimen, if the target $RC \times ECOFF$ is selected, the application may determine and display the DoseECOFF dosing regimen, if the target $RC \times ECOFF_{max}$ is selected, the application may determine and display the DoseECOFF_{max} dosing regimen, if the
20 target $RC \times ECOFF_{cut}$ is selected, the application may determine the DoseECOFF_{cut} dosing regimen, if the target C_{rap} is selected, the application may determine and display the DoseRap dosing regimen and if the target C_{lim} is selected, the application may determine and display the Doselim dosing regimen.

The calculation of a dosing regimen to reach a target may comprise
25 several consecutive simulations each with a test dosing regimen, until the last simulation reaches the target. The dosing regimen of the first simulation is obtained by modifying the current dosing regimen applied to the patient 2. The dosing regimen of the next simulation is obtained by modifying the dosing regimen of the previous simulation.

30 Preferably, only the dose is increased for obtaining the dosing regimen of each of one or several first simulations, the dose interval and the infusion duration being left unchanged. The dose is for example increased until the target can be

reached or until the dose reaches a predefined limit. In the latter case, the dose interval is decreased for obtaining the dosing regimen of each of one or several following simulations, the dose and the infusion duration being left unchanged. The dose interval is for example decreased until the target can be reached or
5 until the dose interval reaches a predefined limit. In the latter case, the dose can be adjusted with this new dose interval until the target can be reached. If not, only the infusion duration is increased for obtaining the dosing regimen of each of one or several following simulations, the dose and the dose interval duration being left unchanged. The infusion duration can be increased until obtaining a
10 continuous infusion. If the target can still not be reached, the dose is also modified.

Preferably, only the dose and the dose interval can be modified for time and concentration-dependent antibiotics, while only the dose, the dose interval and the infusion duration can be modified for time dependent antibiotics.

15 In some embodiments, the application may, at a fourth comparison step S4, compare the limit concentration C_{lim} to a residual concentration determined by a simulation using the dosing regimen to reach one of the possible targets. In this case, this dosing regimen may be calculated in advance (before selection of target(s)).

20 The comparison steps S1 and/or S2 and/or S3 and/or S4 provide sets of inequalities between PPE, C_r and possible target(s), respectively forming comparison results. At least some of the comparison results are respectively associated with one or several possible targets. At least some of the comparison results correspond to a satisfactory current dosing regimen and therefore
25 associated with no possible target.

Referring to **figure 5**, an example of decision tree for carrying out the comparison steps S1, S2, S3 is illustrated, in the case of a time dependent antibiotic with identified bacteria and unknown MIC.

In the described example, the decision tree is a binary decision comprising
30 nodes at each of which one inequality is tested.

The comparison steps S1 and/or S2 and/or S3 are implemented in the nodes of the decision tree and provide the sets of inequalities between PPE, C_r

and possible target(s), respectively forming the comparison results (referenced Rfn, with f the figure number and n = 01, 02, 03, ... , 10, 11, etc.). The possible target(s) associated with at least some of the comparison results are indicated in leaves of the decision tree. The satisfactory comparison results are indicated, on
5 figure 5, by "OK" in the corresponding leaf.

As illustrated on figure 5, the comparison result R04 corresponds to CE<Crap, Cr>Crap, Cr<Ctox and Cr>Clim and is associated with the reported concentration Crap. Similarly, the result R12 corresponds to CE>Crap, Cr>CE, Cr>Ctox and CE>Clim and is associated with the efficiency target CE =
10 RCTxECOFF and Clim.

Therefore, in the described example, the possible target(s) selected by the application are the one(s) associated with the comparison result provided by the comparison steps with the values for the current treatment (i.e. the values of Cr, RCT, ECOFF Crap, Ctox, Clim).

15 It is further apparent that the application may determine (for example at step E13) a dosing regimen for each selected target. In the example of figure 5, if the comparison result for the current treatment is the comparison result R04, the dosing regimen DoseRap is determined in order to try to make the residual concentration Cr reach the reported concentration Crap. If the comparison result
20 for the current treatment is the comparison result R12, the dosing regimen DoseECOFF is determined in order to try to make the residual concentration Cr reach the epidemiological cut off values ECOFF and the dosing regimen DoseLim is determined in order to try to make the residual concentration Cr reach the limit concentration.

25 Furthermore, as explained previously, each comparison result is preferably associated with a recommendation message to be displayed by the application (preferably after dose limitation according to step E15), the message comprising each determined dosing regimen as well as, for example, specific comments corresponding to the comparison result (for example, a warning that
30 the residual concentration Cr is higher than the toxic concentration Ctox and/or information indicating the percentage of annihilated strains of bacteria as described previously).

The physician may then choose one of the recommended displayed dosing regimen(s) to treat the patient 2.

Figure 6 is a figure similar to figure 5, in the case of a time dependent antibiotic with identified bacteria and known MIC.

5 **Figure 7** is a figure similar to figure 5, in the case of a time dependent antibiotic with unknown bacteria.

Figure 8 is a figure similar to figure 5 for carrying out the comparison steps S1, S2, S4, in the case of a time and concentration dependent antibiotic with identified bacteria and known MIC.

10 In particular, comparison step S4 comprises comparing the limit concentration C_{lim} to a simulated residual concentration $Cr(DoseMIC)$ supposing that the DoseMIC dosing regimen is applied to the patient 2.

Figure 9 is a figure similar to figure 8, in the case of a time dependent antibiotic with identified bacteria and unknown MIC.

15 In particular, comparison step S4 comprises comparing the limit concentration C_{lim} to a simulated residual concentration $Cr(DoseECOFF)$ supposing that the DoseECOFF dosing regimen is applied to the patient 2.

Figure 10 is a figure similar to figure 8, in the case of a time dependent antibiotic with unknown bacteria.

20 In particular, comparison step S4 comprises comparing the limit concentration C_{lim} to a simulated residual concentration $Cr(DoseECOFF_{max})$ supposing that the DoseECOFF_{max} dosing regimen is applied to the patient 2, and comparing the limit concentration C_{lim} to a simulated residual concentration $Cr(DoseECOFF_{cut})$ supposing that the DoseECOFF_{cut} dosing regimen is
25 applied to the patient 2.

Although the present invention has been described hereinabove with reference to a specific embodiment, the present invention is not limited to this specific embodiment and modifications will be apparent to a person skilled in the art which as falling within the scope of the present invention.

30 In the claims, the word “comprising” does not exclude other elements or steps, and the indefinite article “a” or “an” does not exclude a plurality. The mere

fact that different features are recited in mutually different dependent claims does not indicate that a combination of these features cannot be advantageously used.

List of abbreviations

AUC	Area Under the Curve
CE	Efficiency Target
C _{lim}	Limit Concentration
C _m	Measured Concentration
C _r	Residual Concentration
C _{rap}	Reported Concentration
C _{tox}	Toxic Concentration
ECOFF	Epidemiological Cut-Off value
EUCAST	European Committee on Antimicrobial Susceptibility Testing
MIC	Minimum Inhibitory Concentration
PPE	Efficiency Pharmacokinetic Parameter
SUS	Susceptibility

CLAIMS

1. Method for determining an optimum drug dosing regimen to treat a patient (2) efficiently against at least one drug-sensitive pathogenic agent, said method comprising the following steps:
- 5 - obtaining patient-related data related to said patient (2);
- obtaining a concentration of said drug measured in the patient's body at an arbitrary time ($C_m(t)$);
- from said measured concentration ($C_m(t)$), computing (E1) an estimated
- 10 drug concentration (C3) time-course by using a Bayesian model configured according to :
- an initial dose previously administered to the patient;
 - mean values of parameters selected from said patient-related data
 - interindividual variability of said parameters amongst a population
- 15 of patients;
- said method being characterized in that it further comprises :
- from said estimated drug concentration time-course (C3), determining an efficiency pharmacokinetic parameter (PPE) adapted to said drug and to said patient and a residual drug concentration (C_r);
- 20 - determining possible targets including at least one possible target (C_{rap} , CE) for the efficiency pharmacokinetic parameter (PPE) and one possible target for the residual drug concentration (C_r), defined as the residual drug concentration for which an increased risk of side effects is reported and called increased risk target (C_{lim});
- 25 - a first comparison step (S1) wherein said efficiency pharmacokinetic parameter (PPE) is compared to at least one of the possible target(s) (C_{rap} , CE, CE_{max} , CE_{cut}) for the efficiency pharmacokinetic parameter (PPE);
- a second comparison step (S2) wherein the residual drug concentration (C_r) is compared to a toxic concentration (C_{tox}) defined as a drug concentration
- 30 beyond which serious side effects occur and wherein the residual drug concentration (C_r) is compared to the increased risk target (C_{lim});

- selecting at least one of the possible targets according to the first and second comparison steps S1, S2);
- for each selected target, determining (E13) said optimum drug dosing regimen to treat said patient to reach said selected target.

5

2. Method according to claim 1, comprising a third comparison step (S3) wherein two of the possible targets (CE, Crap, Clim) are compared to each other, and wherein selecting at least one of the possible targets is carried out according to the first, second and third comparison steps (S1, S2, S3).

10

3. Method according claim 1 or 2, comprising obtaining drug data related to said drug and selecting the possible target(s) for the efficiency pharmacokinetic parameter (PPE) from the drug data.

15

4. Method according to claim 3, wherein the drug data indicates that the drug is an identified antibiotic for a bacteria.

5. Method according to claim 4, wherein at least one of the possible target(s) (CE) for the efficiency pharmacokinetic parameter (PPE) is defined as the product of a target ratio (RC) and a susceptibility factor (SUS) relative to said bacteria, wherein the target ratio (RC) is defined as the ratio to be reached to improve the drug efficiency based on known relationships between drug concentration and efficiency.

25

6. Method according to claim 5, further comprising receiving bacteria data identifying the bacteria and wherein the susceptibility factor (SUS) is a minimal inhibiting concentration (MIC) of this identified bacteria or an epidemiological cut-off value (ECOFF) of this identified bacteria.

30

7. Method according to claim 6, further comprising computing and displaying a value of a percentage of sensitive strains of the identified bacteria which can be annihilated by the measured drug concentration if, according to the

first comparison step (S1), the efficiency pharmacokinetic parameter (PPE) is strictly less than the possible target (CE) defined as the product of the target ratio (RC) for the identified antibiotic and the susceptibility factor (SUS) being the epidemiological cut-off value (ECOFF) of the identified bacteria.

5

8. Method according to claim 5, further comprising receiving bacteria data indicating that the bacteria is unknown and wherein the susceptibility factor (SUS) is a maximum epidemiological cut-off value (ECOFF_{max}) adapted to combat all bacteria that are usually sensitive and for which an epidemiological cut-off value (ECOFF) is known or a reduced epidemiological cut-off value (ECOFF_{cut}) for an empirical treatment adapted to combat most pathogenic agents excluding species having the highest epidemiological cut-off values (ECOFF) according to known minimal inhibiting concentration distributions.

15 9. Method according to claim 8, further comprising computing and displaying, for each of a predefined number of possible bacteria, for example at least two predefined bacteria, a value of a percentage of sensitive strains of said possible bacteria which can be annihilated by the measured drug concentration of drug if, according to the first comparison step (S1), the efficiency pharmacokinetic parameter (PPE) is strictly less than the efficiency target (CE_{max}) defined as the product of the target ratio (RC) for the identified antibiotic and the susceptibility factor (SUS) being the maximum epidemiological cut-off value (ECOFF_{max}).

25 10. Method according to any one of claims 4 to 9, wherein the identified antibiotic is time dependent and wherein the efficiency pharmacokinetic parameter (PPE) is the residual drug concentration (Cr).

30 11. Method according to claim 10, wherein one of the possible target(s) for the efficiency pharmacokinetic parameter (PPE) is a reported concentration (C_{rap}) for said identified antibiotic.

12. Method according to any one of claims 4 to 9, wherein the identified antibiotic is time and concentration dependent and wherein the efficiency pharmacokinetic parameter (PPE) is an area under the curve (AUC) of said estimated drug concentration time-course (C3).

5

13. Method according to any of the preceding claims, comprising a control step (E15) wherein, in the determined optimum drug dosing regimen:

- the dose is increased by not more than 50% of said initial dose, except if the dose is lower than a maximal dose recommended for said drug ; and/or

10 - the dose is decreased by not more than 50% of said initial dose, except if the dose is greater than said maximal recommended dose.

14. Method according to any of the preceding claims, wherein the optimum drug dosing regimen is obtained as a result of modifying the dose and/or the dose
15 interval for time and concentration-dependent antibiotics, or the dose, the dose interval and/or the duration of infusion for time dependent antibiotics.

15. System comprising an application server (4) and a client terminal (3), characterized in that said client terminal (3) or said application server (4) is
20 adapted to implement the method according to any one of claims 1 to 14.

16. System according to claim 12, characterized in that it further comprises a patient database (5) from which the client terminal (3) and/or the application server (4) is adapted to retrieve patient-related data.

25

17. System according to claim 12 or 13, characterized in that it further comprises a third-party database (6) from which the client terminal (3) and/or the application server (4) is adapted to retrieve information on pathogenic agents and/or information on drug interactions.

30

18. Computer programme comprising instructions adapted to implement the steps of the method according to any one of claims 1 to 14 when the programme is executed on a computer (3).

- 5 19. Medium for storing information, removable or not, readable by a computer (3) or a microprocessor (3.1) and comprising code instructions of a computer programme adapted for implementing the steps of the method according to any one of claims 1 to 14, when said programme is executed by a computer.

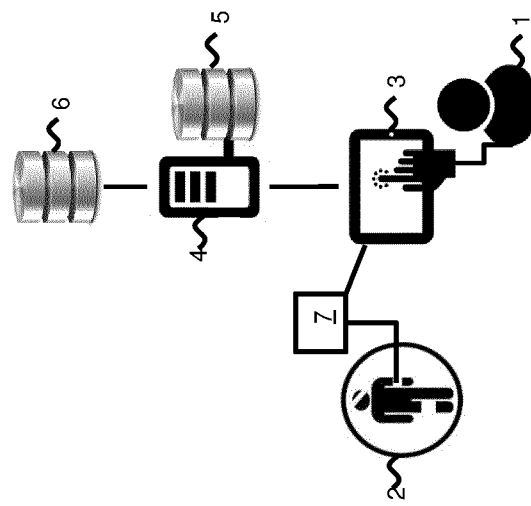


Fig. 1

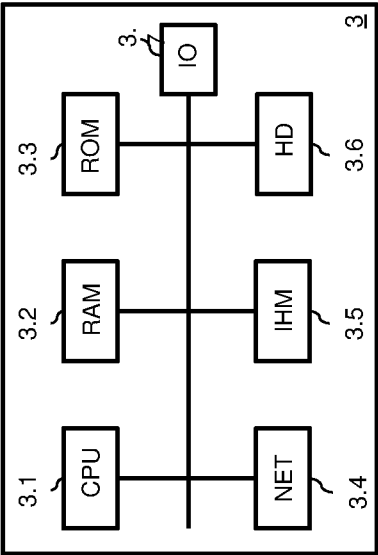


Fig. 2

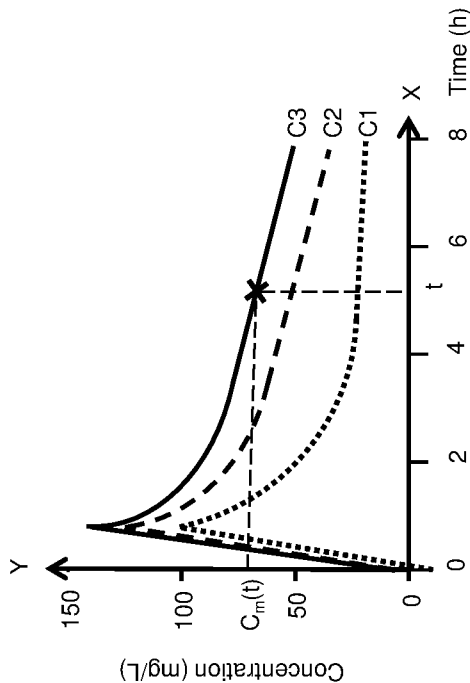


Fig. 3

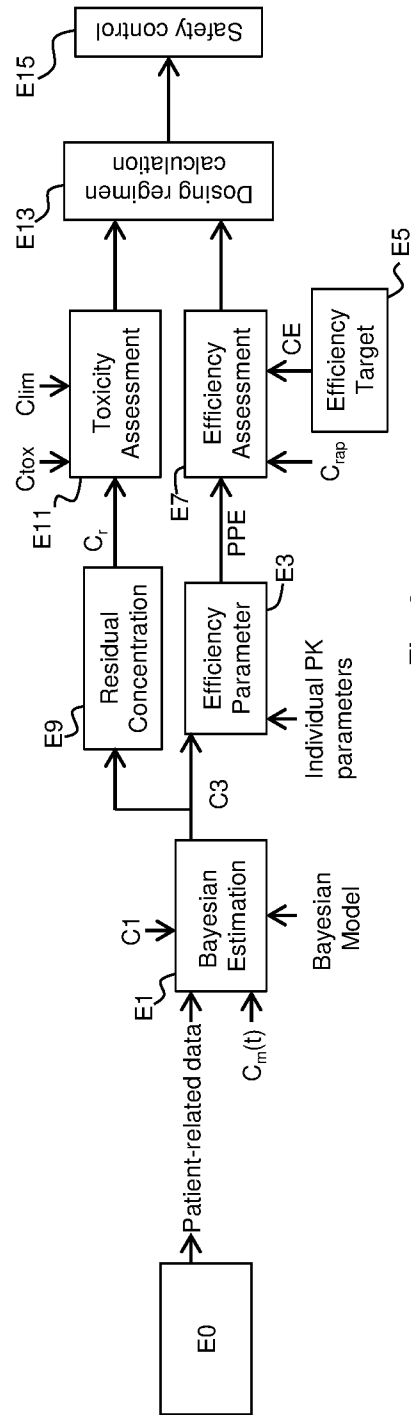
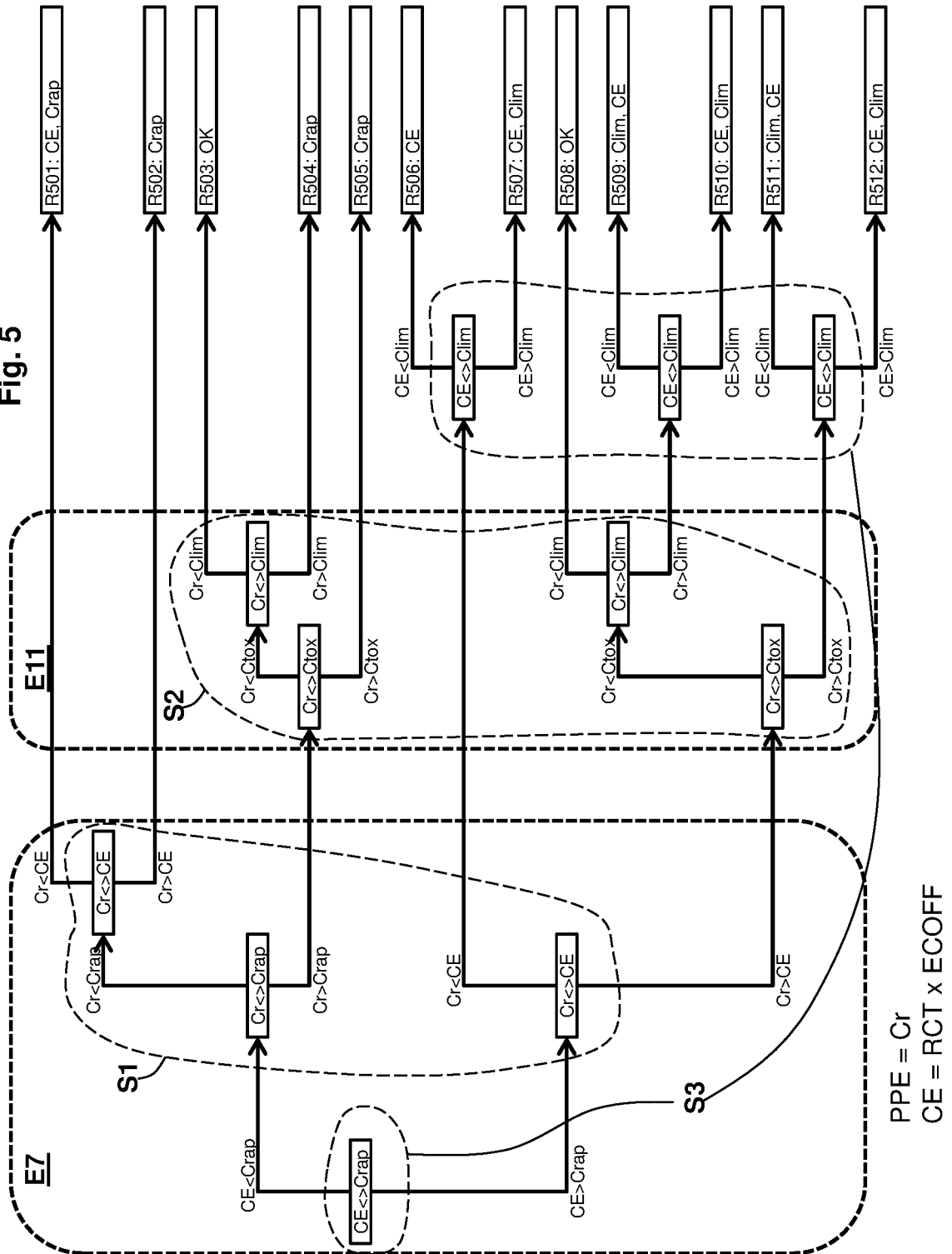
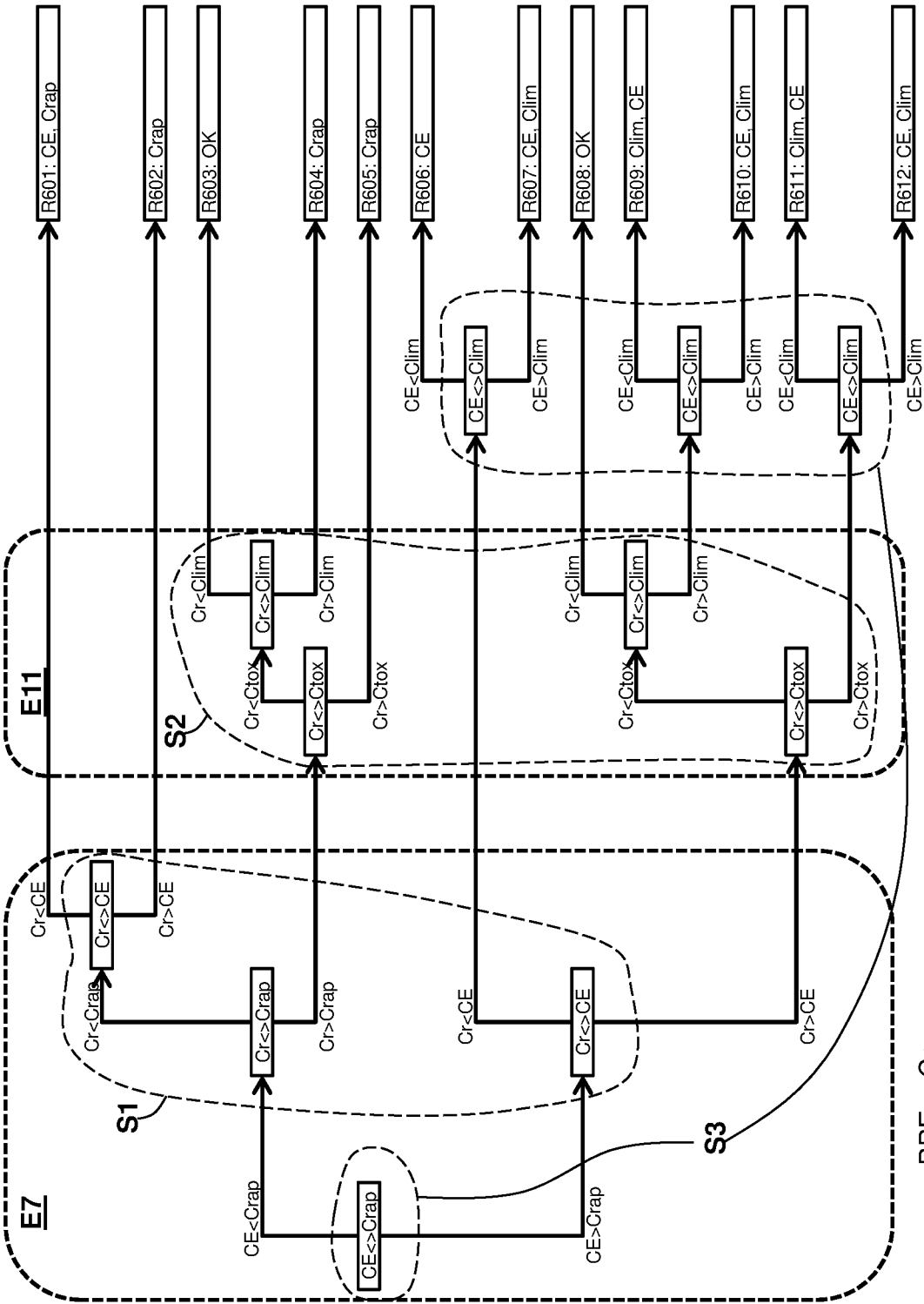


Fig. 4

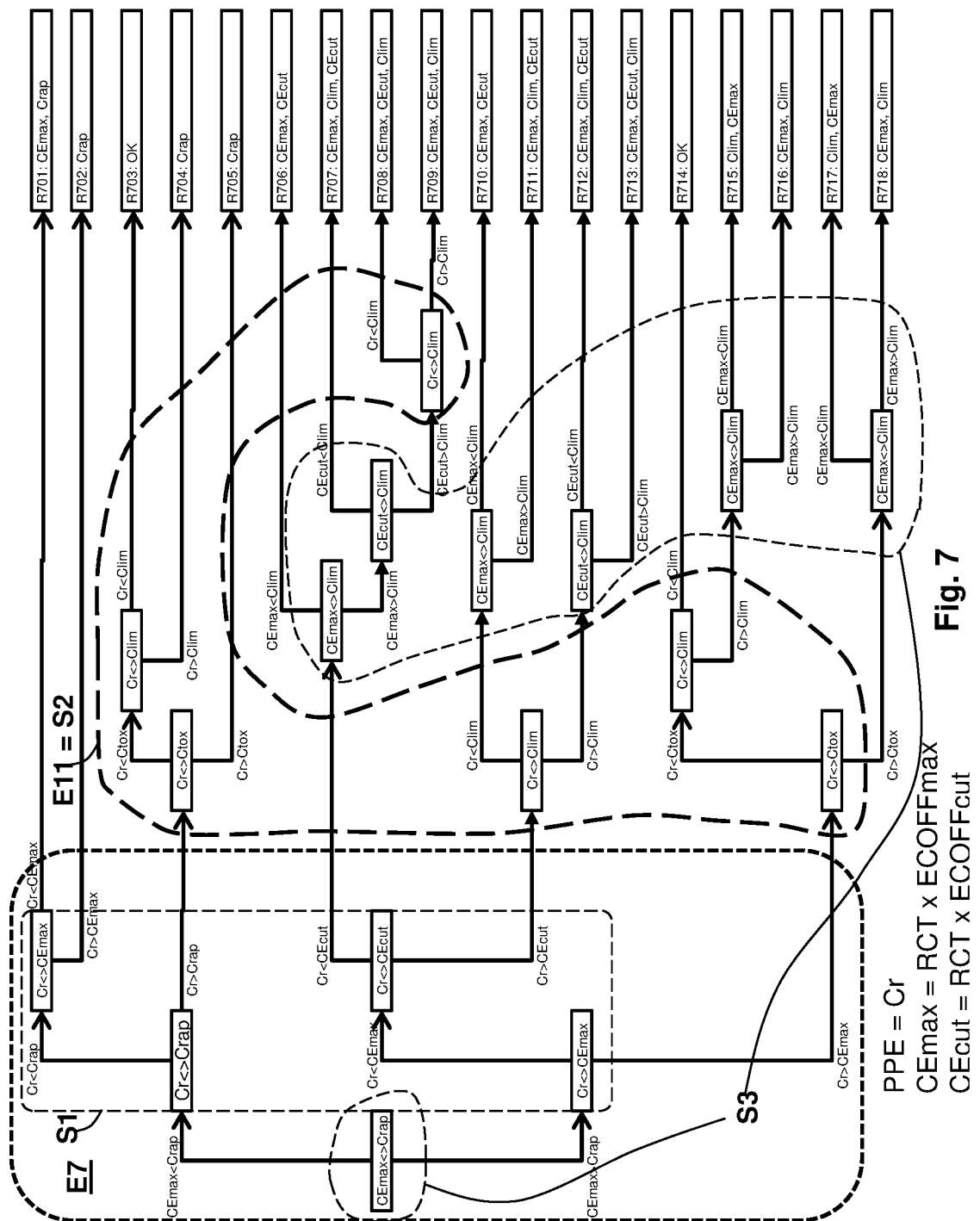
Fig. 5





PPE = Cr
CE = RCT x MIC

Fig. 6



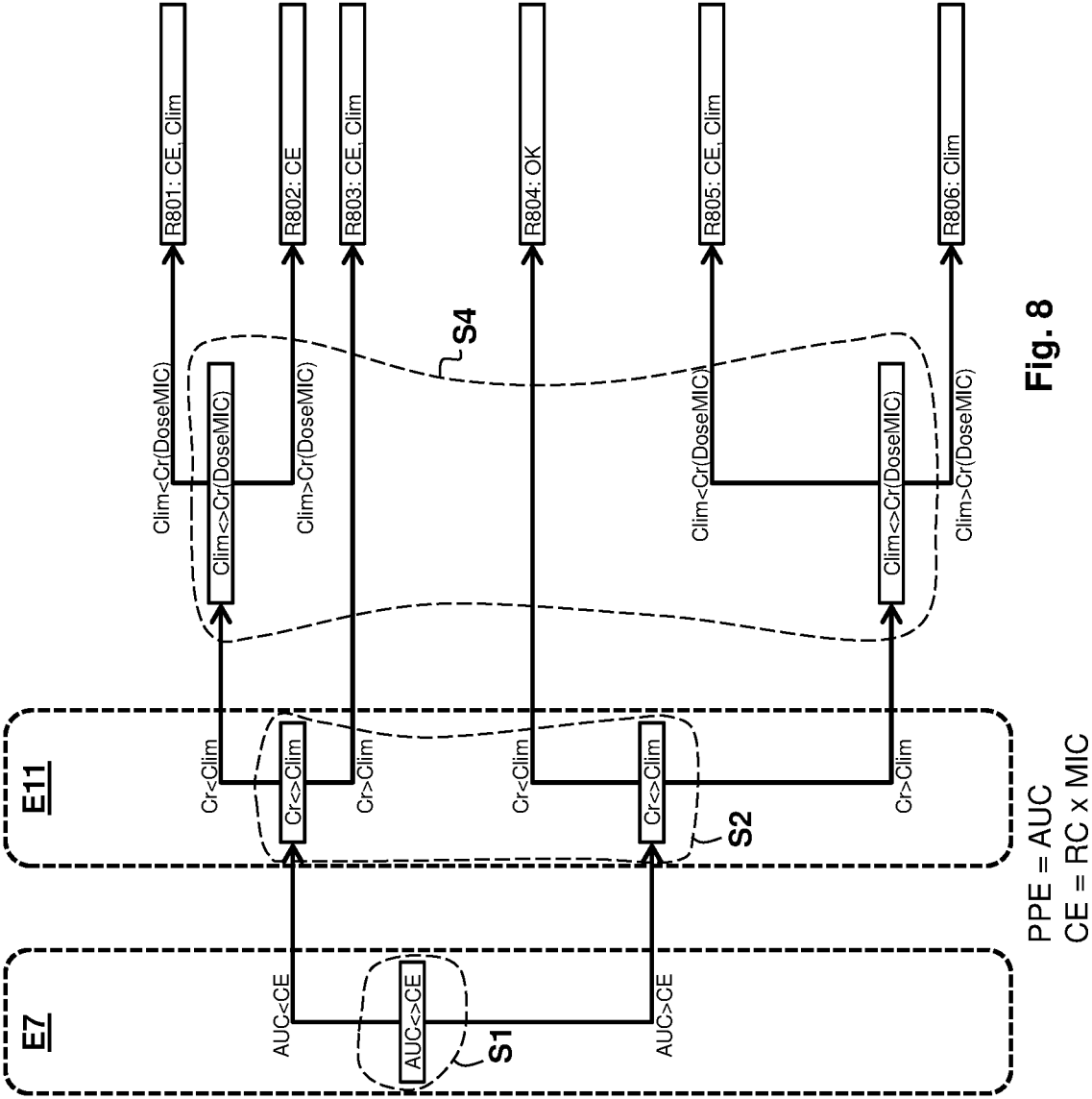


Fig. 8

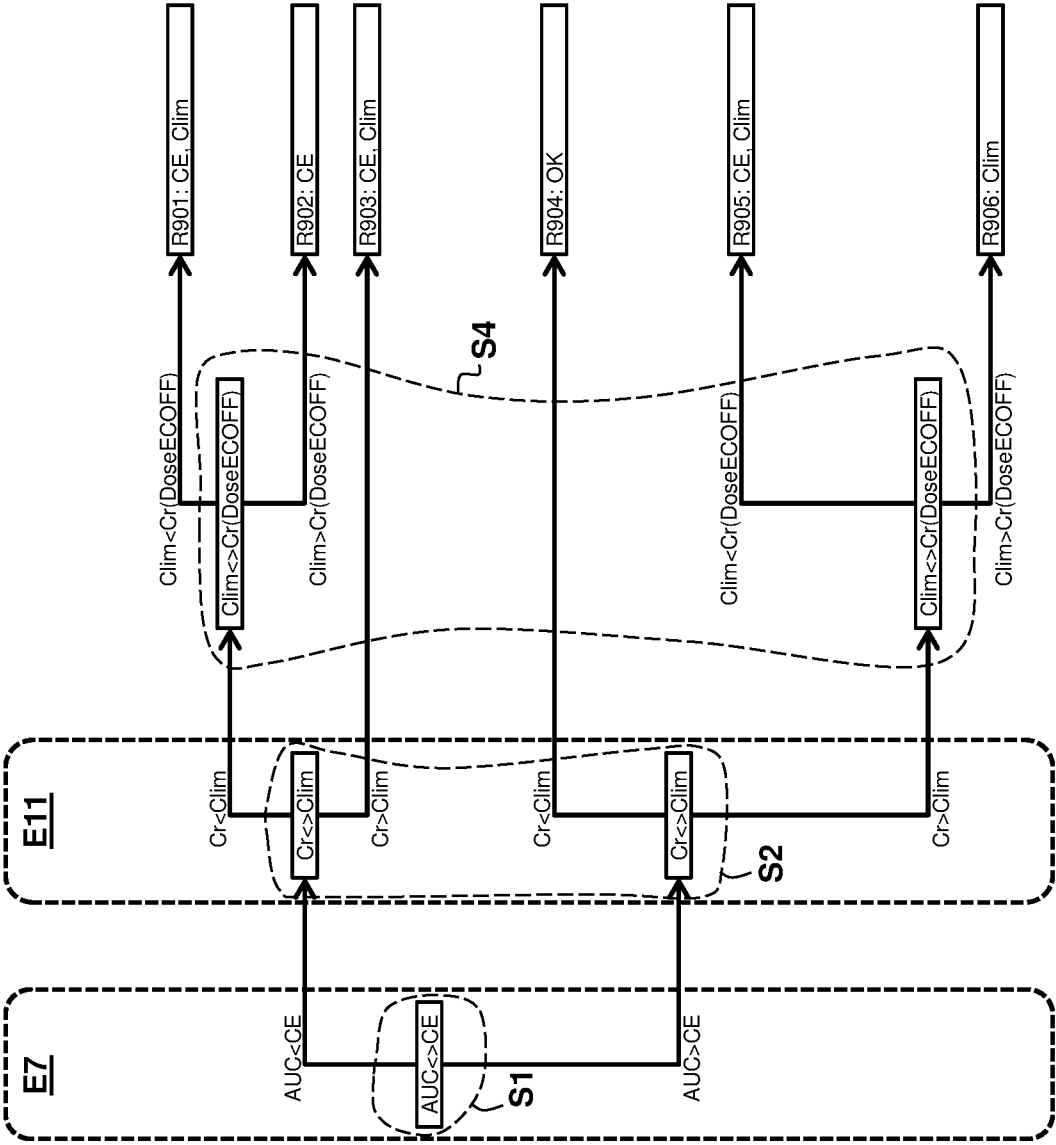
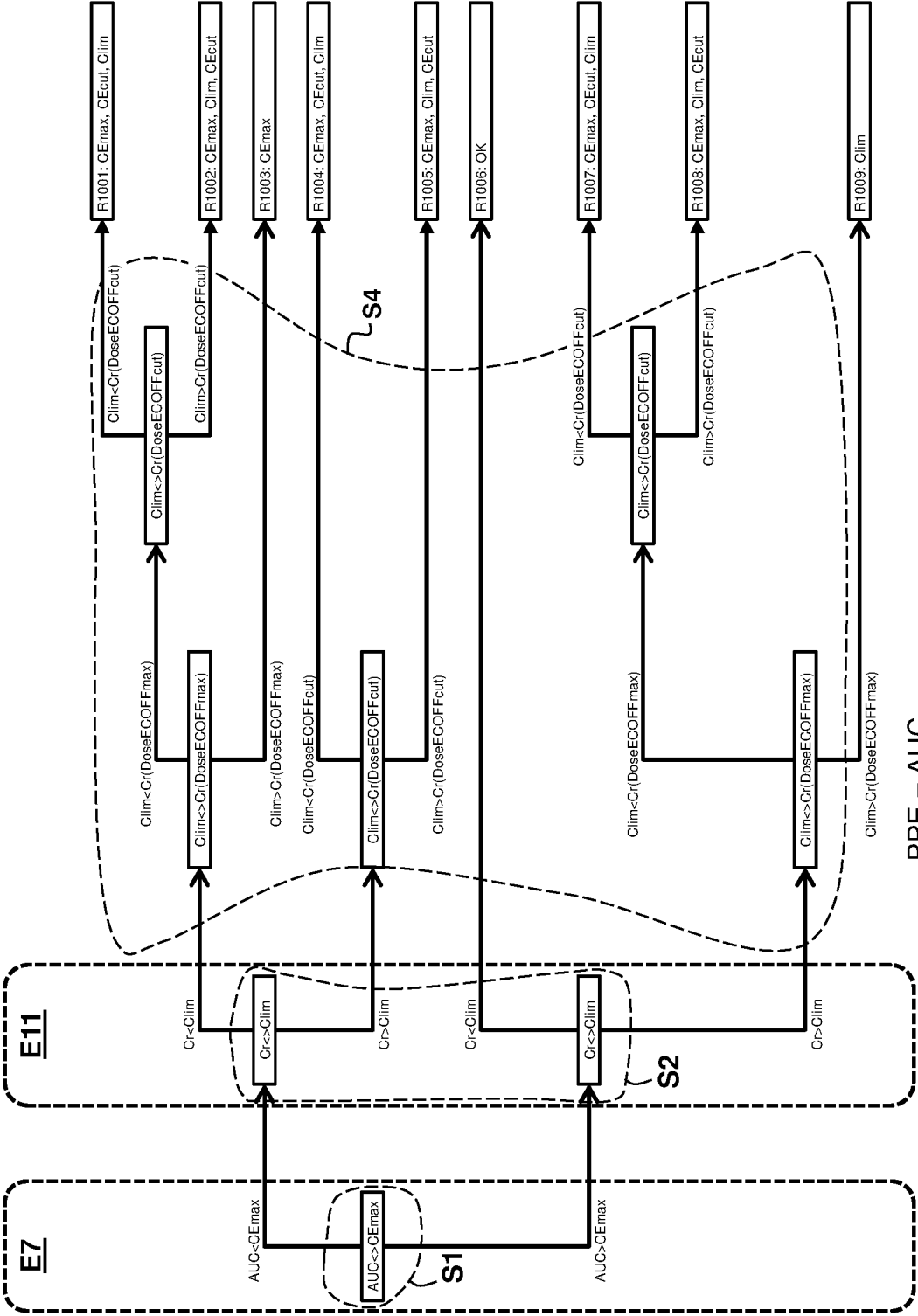


Fig. 9 PPE = AUC
CE = RC x ECOFF



PPE = AUC
CEmax = RC x ECOFFmax
CEcut = RC x ECOFFcut

Fig. 10

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/065831

A. CLASSIFICATION OF SUBJECT MATTER INV. G06N7/00 G06N3/00 G06J1/00 C40B50/00 G16C20/00 G16H10/00 G16H20/00 ADD. According to International Patent Classification (IPC) or to both national classification and IPC											
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) G06N G06J G06F C40B G16C G16H Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, BIOSIS, EMBASE, WPI Data											
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category*</th> <th style="width: 70%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width: 20%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">X</td> <td style="vertical-align: top;"> FAUCHET FLORIS ET AL: "Population Pharmacokinetics Study of Recommended Zidovudine Doses in HIV-1-Infected Children", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 57, no. 10, October 2013 (2013-10), pages 4801-4808, XP002800255, see the freetext sheet of the WO-ISA ----- </td> <td style="text-align: center; vertical-align: top;">1-19</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">X,P</td> <td style="vertical-align: top;"> MANGIN OLIVIER ET AL: "Free prednisolone pharmacokinetics predicted from total concentrations in patients with inflammatory - immunonologic conditions", FUNDAMENTAL & CLINICAL PHARMACOLOGY, vol. 34, no. 2, April 2020 (2020-04), XP002800256, see the freetext sheet of the WO-ISA ----- -/-- </td> <td style="text-align: center; vertical-align: top;">1-10</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	X	FAUCHET FLORIS ET AL: "Population Pharmacokinetics Study of Recommended Zidovudine Doses in HIV-1-Infected Children", ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, vol. 57, no. 10, October 2013 (2013-10), pages 4801-4808, XP002800255, see the freetext sheet of the WO-ISA -----	1-19	X,P	MANGIN OLIVIER ET AL: "Free prednisolone pharmacokinetics predicted from total concentrations in patients with inflammatory - immunonologic conditions", FUNDAMENTAL & CLINICAL PHARMACOLOGY, vol. 34, no. 2, April 2020 (2020-04), XP002800256, see the freetext sheet of the WO-ISA ----- -/--	1-10
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☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.											
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Date of the actual completion of the international search 10 September 2020		Date of mailing of the international search report 29/09/2020									
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Albayrak, Timur									

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2020/065831

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	TAUZIN MANON ET AL: "Simulations of Valproate Doses Based on an External Evaluation of Pediatric Population Pharmacokinetic Models", JOURNAL OF CLINICAL PHARMACOLOGY, vol. 59, no. 3, March 2019 (2019-03), pages 406-417, XP002796312, Page 407 r-col under "Methods": extraction of patients' data, including data for serum drug concentrations (feature Ctm) Page 407 r-col under "Valproate Concentration Assay": assessment of valproate concentrations Page 410 l-col under "Evaluation of Dosing Schemes": Bayesian estimation to determine required doses to achieve target concentrations. Intermatent variabilities are taken into account (see page 412 l-col last paragraph) Page 411 r-col under "Evaluation of Dosing Schemes": Forecast of trough concentrations for the patients. Page 412 l-col paragraph 2: Determination of most appropriate concentrations. -----	1-19