



Tucuxi Instructions for Use

Release 1.0

Tucuxi dev team

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1

Introduction

Tucuxi is a software developed to assist the analysis of drug concentration in blood used for therapeutic drug monitoring in clinical pharmacology.

The analysis depends on the administered drug, on the patient's specific set of parameters and on the patient's state during the blood sampling. Computing methods varies between different route administration drug and model chosen.

Tucuxi allows to gather those data and provides proper dosages adjustments for the treatment analysis of each individual. The software generates graphical informations on the concentrations measured and predicted, given the patient's covariates and targets figured by the specialist.

The process of a treatment analysis with Tucuxi is presented as a flow gathering different steps. The interface of the software is separated in three parts, including the process panel on the top, allowing to navigate between steps. The two parts below is used to apply changes or set parameters with the control panel and to display informations about the measured concentration to analyze in the graph area. After the specialist's validation, a report is generated and presents every element necessary to the therapeutic drug monitoring of a patient.

The software is developed and maintained by the REDS institute, from the HEIG-VD in collaboration with the CHUV.

2

Installation

3.1 Start Menu

To start the treatment of a request, select the **Pending request** icon. The list of requests appears. Some filters situated above the list allows you to display only the specific kind of request wanted. Clicking on a title of the table allows you to list the requests depending on the order desired.

To continue the treatment analysis of a patient, select the **Load interpretation** icon. The list of patients appears. Some filters situated above may help you to find the concerned patient. Clicking on a table heading allows you to list the requests depending on the order desired.

To start an analysis treatment with a new patient, select the **New Patient** icon.



3.2 1. Patients

This first step displays and allows to register several informations about the selected patient.

To register the new patient, completing the **Patient required information** section is necessary. Extra informations can be provided in the section below. You can also indicate who is the physician in charge.

Welcome to Tucuxi! Graphs of predicted concentrations will be shown here..

PATIENT REQUIRED INFORMATION

First name:	Demo Patient John	Last name:	Doe
Birth date:	01/01/1960	Gender:	<input checked="" type="radio"/> Male <input type="radio"/> Female

PATIENT EXTRA INFORMATION

Identifier:	P001	Stay number:	S001
Address:	Avenue de Lausanne 1		
City:	Genève	Postcode:	1000
State:	GE	Country:	Switzerland

3.3 2. Drugs

General informations on the drug used for the current analysis treatment is displayed here.

For a new patient, select the drug subject to the analysis under the **Active substance** section on the control panel. Informations on the **Domain** of the selected drugs will appear. The related **study** about the population pharmacokinetic model for each choice is also provided.

3.4 3. Dosages

The **Dosages history** section on the control panel presents every dosage registered, previously given to the patient. On the graph panel, population percentiles are displayed. These percentiles describe the variability of blood drug levels expected in the target population taking into account the chosen dosage.

Go to the next step if no dose have been administrated to the new patient yet.

Tucuxi

Demo Patient John Doe
1960-01-01T00:00:00

Imatinib

ACTIVE SUBSTANCE

Imatinib

Imatinib

Model: ezechiel.model.linear.1comp.extra.dv
ATC: L01XE01
Brands: Glivec
Domain: Adult, (Disease: CML and GIST, Age range: 20-88 yrs, Weight range: 44-110kg, AGP plasma concentration range: 0.4-2.0 g/L)
Study: Based on Widmer et al. Br J Clin Pharmacol 2006, validated by Gotta et al. Clin Pharmacokinet 2012
Absorption, distribution, metabolism, and excretion
Intake: EXTRa
Distribution: 1 compartments
Elimination: linear

DOMAIN

Adult, (Disease: CML and GIST, Age range: 20-88 yrs, Weight range: 44-110kg, AGP plasma concentration range: 0.4-...

STUDY

Based on Widmer et al. Br J Clin Pharmacol 2006, validated by Gotta et al. Clin Pharmacokinet 2012

TUCUXI

Demo Patient John Doe
1960-01-01T00:00:00

Imatinib

DOSAGES HISTORY

From: 14.01.2018 09:01 To: 14.03.2019 09:01 Dose: 400 mg Interval: 24 hours Infusion:

Dosage parameters

Dose: 400.00 mg
Interval: 24 hours
Route: EXTRa
 At steady state?
Last dose: 14/03/2018 at: 09:01
Ok Apply Cancel

Population **Pop. percentiles (5-25-75-95)**

3.5 4. Covariates

The **Drug covariates list** displays the list of every covariate relevant to the treatment analysis according to the study selected in the “drug” tab. Each selected covariate presents a **Patient variate history** situated in the section below.

Set a value for each covariate by selecting them in the list at first and then, click on the plus symbol in the right of the **Patient variate history** section. A window corresponding to the variate appears with the information fields to complete. If the patient is being registered for the first time, each variate with no history must be set to complete the treatment analysis.

Apriori percentiles are displayed on the graph panel. These percentiles describe the variability of blood drug levels expected in a population that would have the same patient characteristics (covariate values), taking into account the previously chosen dosage.

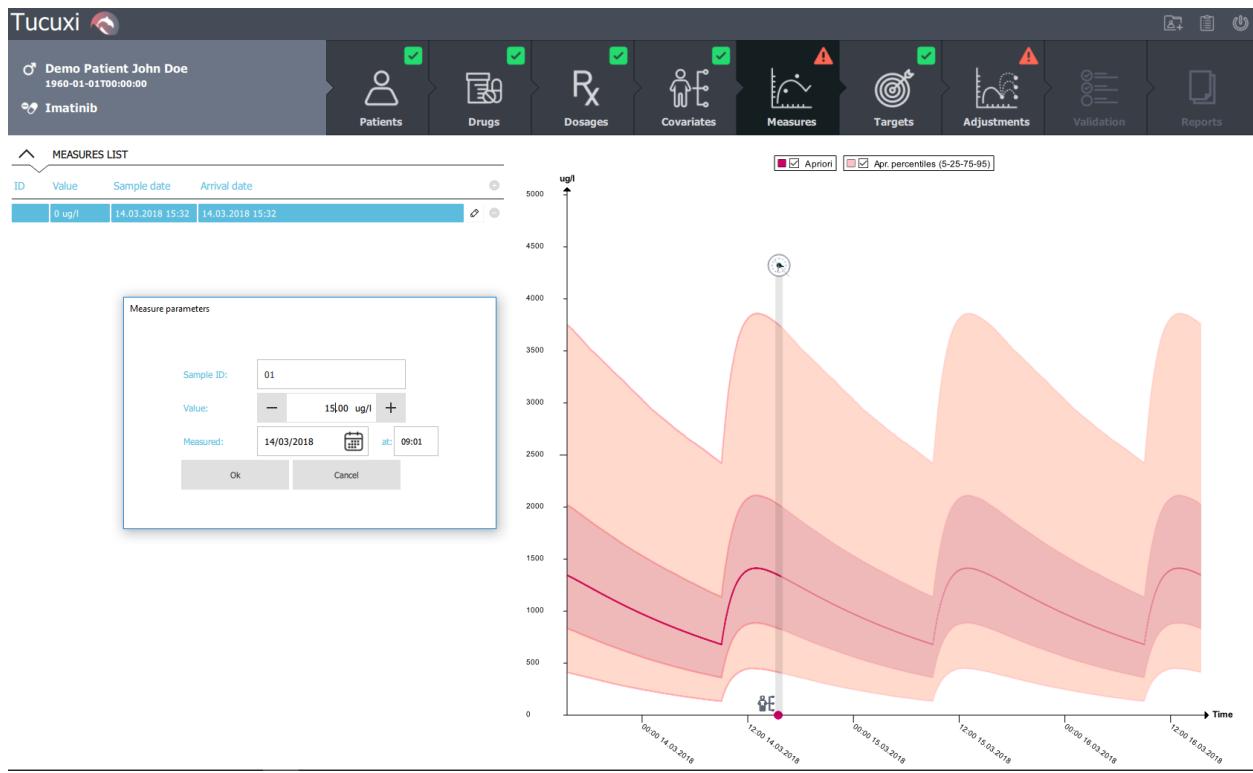


3.6 5. Measures

The **Measures list** allows to add the drug concentration of the sample subject to the analysis by clicking on the plus symbol on the top right corner of the list. A window with informations to fill will appear.

On the graph panel, aposteriori percentiles are displayed. These percentiles describe the variability of blood drug levels expected in a population that would have the same patient characteristics (covariate values), taking into account the previously chosen dosage and the blood level(s) measured.

Go to the next step if no measure of the analyzed drug concentration in blood has been done for the patient yet.



3.7 6. Targets

The **Targets** list displays the maximum, the minimum and the best concentration to obtain for the patient according to the lastest informations found in the scientific literature. Those informations are editable with the pen symbol in the right of each target and additionnal target can be set with the plus symbol. A window with informations to complete will appear.

On the graph area, ideal value of the target are indicated with black crosses and the interval between the minimum and the maximum value is shaded in grey if the residual, mean or peak target is selected.

3.8 7. Adjustments

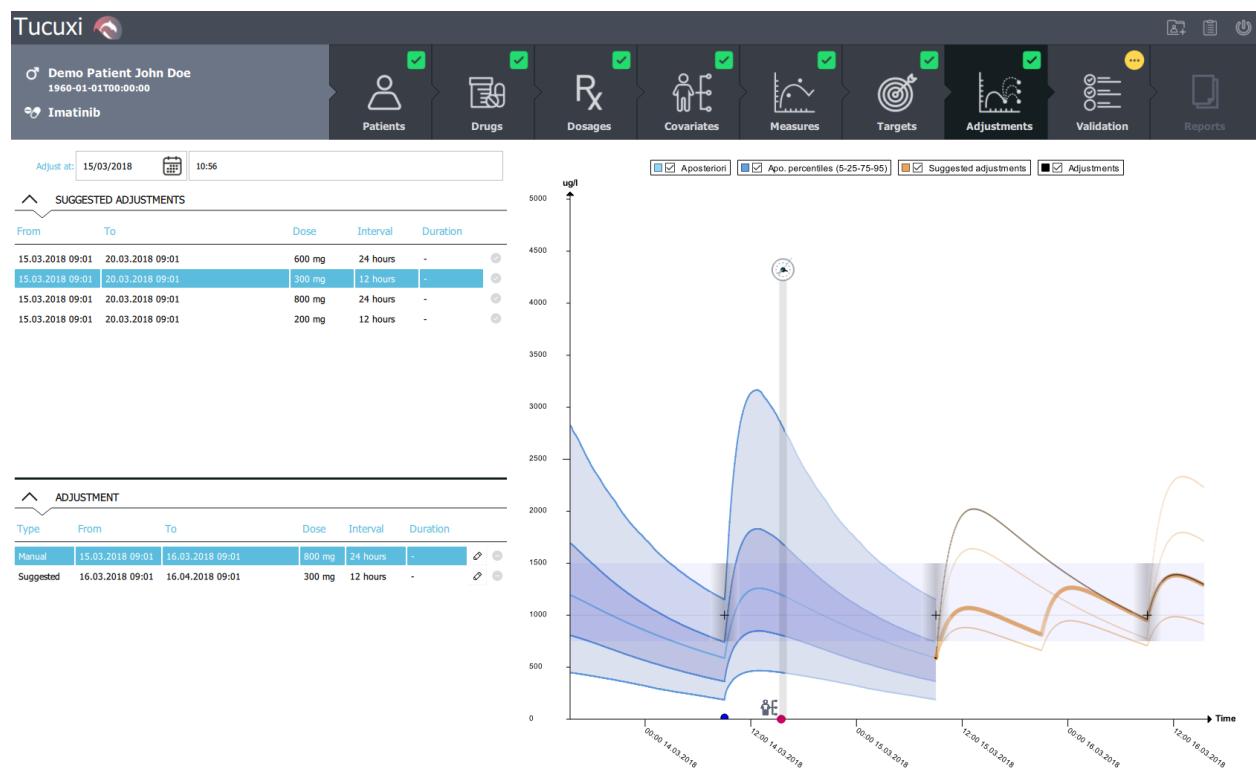
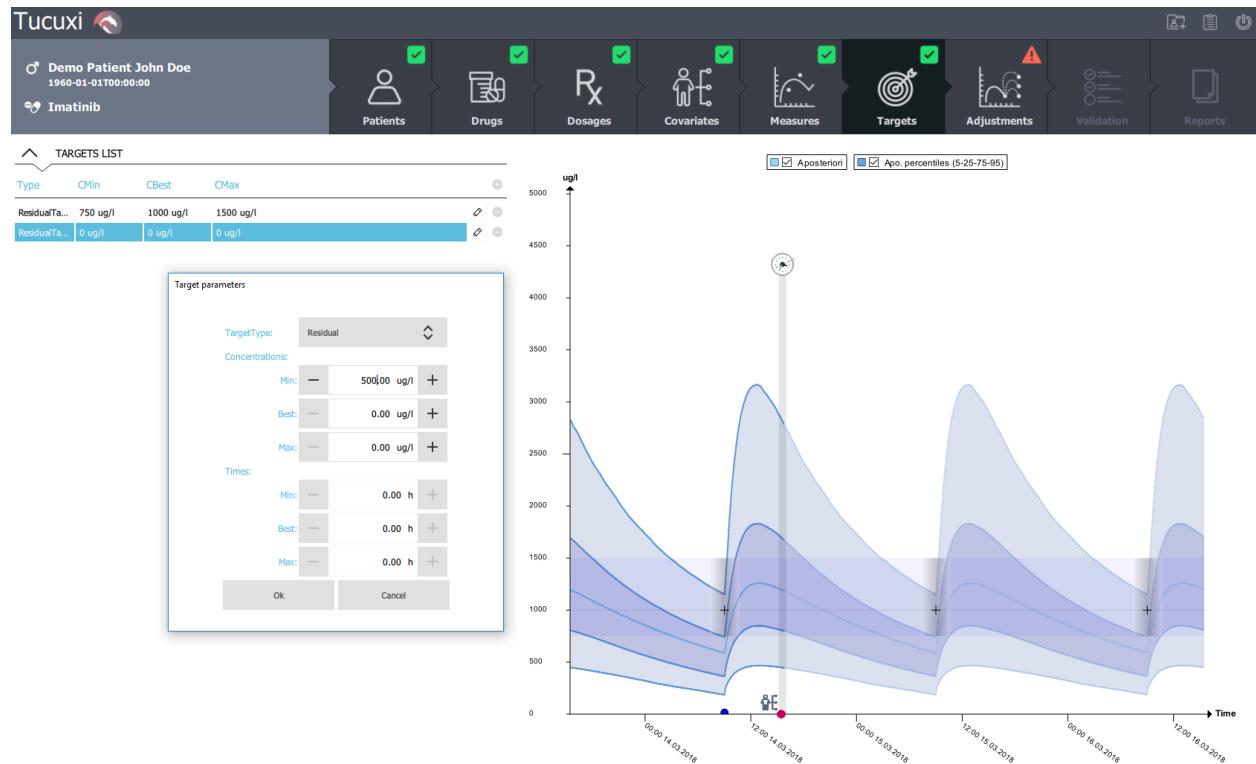
Suggested adjustments are listed in the first section. The **Adjustment** section below is used to set and displays the dosage of drugs to administrate to the patient.

A loading dose can be manually set by checking the box above the **Suggested adjustment** section. Likewise, you can set a rest period if you want to skip takes.

A suggested adjustment can be selected by clicking on the checked symbol on the right of the chosen dosage in the **Suggested adjustments** section

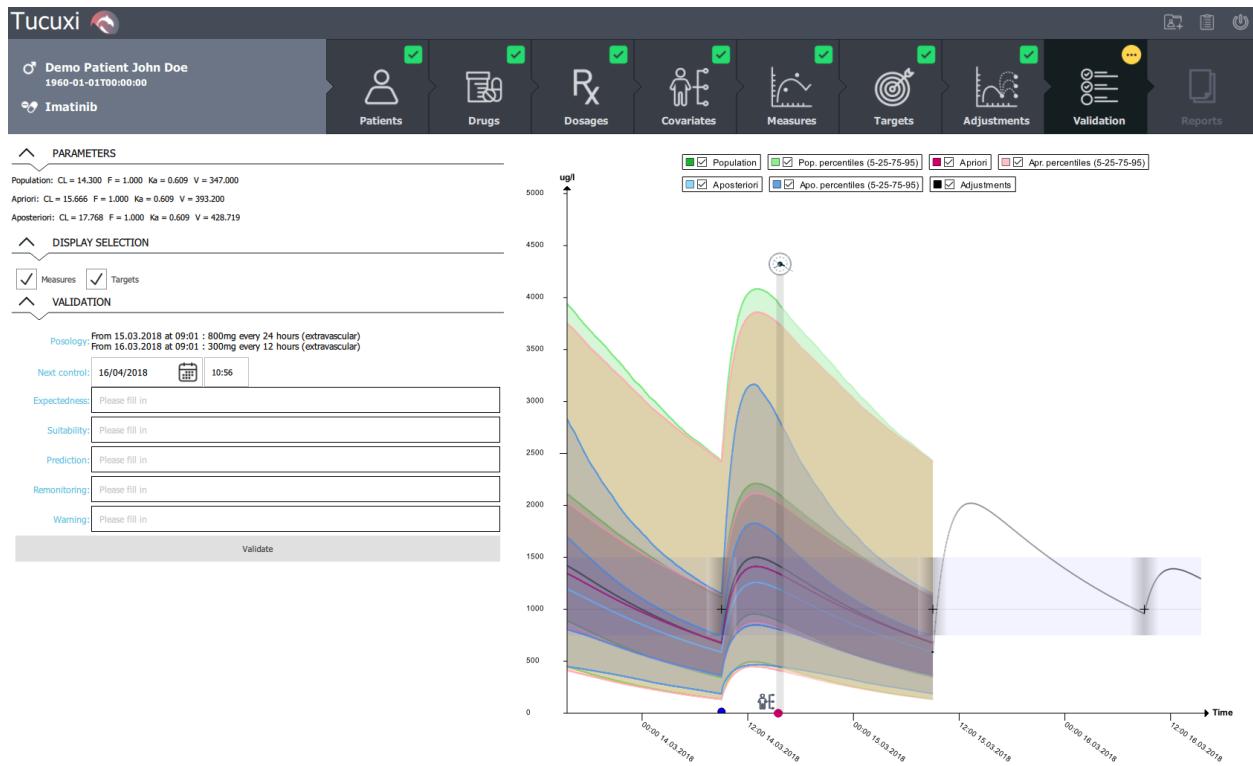
The date and hour of the time when the adjustment is made is shown and editable above the two sections.

Every expected curve of the adjustment is displayed in the graph area on the right panel.



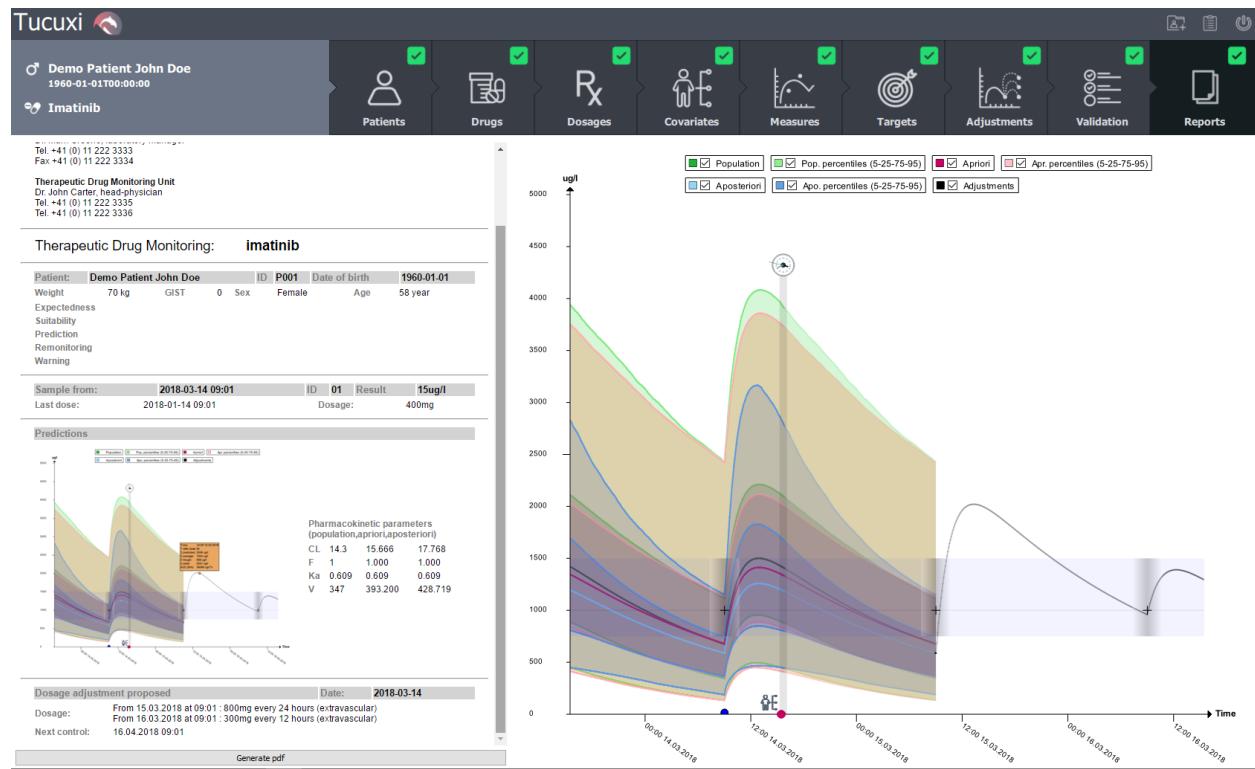
3.9 8. Validation

The **Parameters** section indicates informations about the parameters of the calculation model. The **Validation** section informs about the final dosage chosen and is used to comment the treatment. Click on *Validate* after the checking of every element to end the treatment analysis.



3.10 9. Reports

The final report of the treatment analysis is shown on the right of the interface, with every element needed. Generating a pdf is possible by clicking on the button below the report.



4.1 Start Menu

From the start menu you can start a treatment analysis with a new patient or access treatments analysis in progress or treat the requests from external institution in case Tucuxi is connected to another information system.

The **New Patient** icon leads to the process of a new patient registration and the start of a new treatment analysis.

The **Load interpretation**** icon displays the list of patients already registered. Finding treatments analysis of a specific drug is possible with the drug filter situated above the list. Other filters are available on the right in addition to the refresh button which updates the list. Clicking on a table heading allows to list the requests depending on the order desired. By default, the list is displayed by patient's ID order.

The **Pending requests** icon gives access to requests sent to Tucuxi. Depending of the software version used, treatment requests may provide data automatically set such as the patient's required informations, the drug subjects to the analysis, the history dosages administrated and the measured drug concentration in the sample.

The **Shutdown** icon and the icons mentioned above are accessible anytime during the use of the software, on the top right corner of the interface.

4.2 Interface general informations

The interface of Tucuxi is separated in three parts.

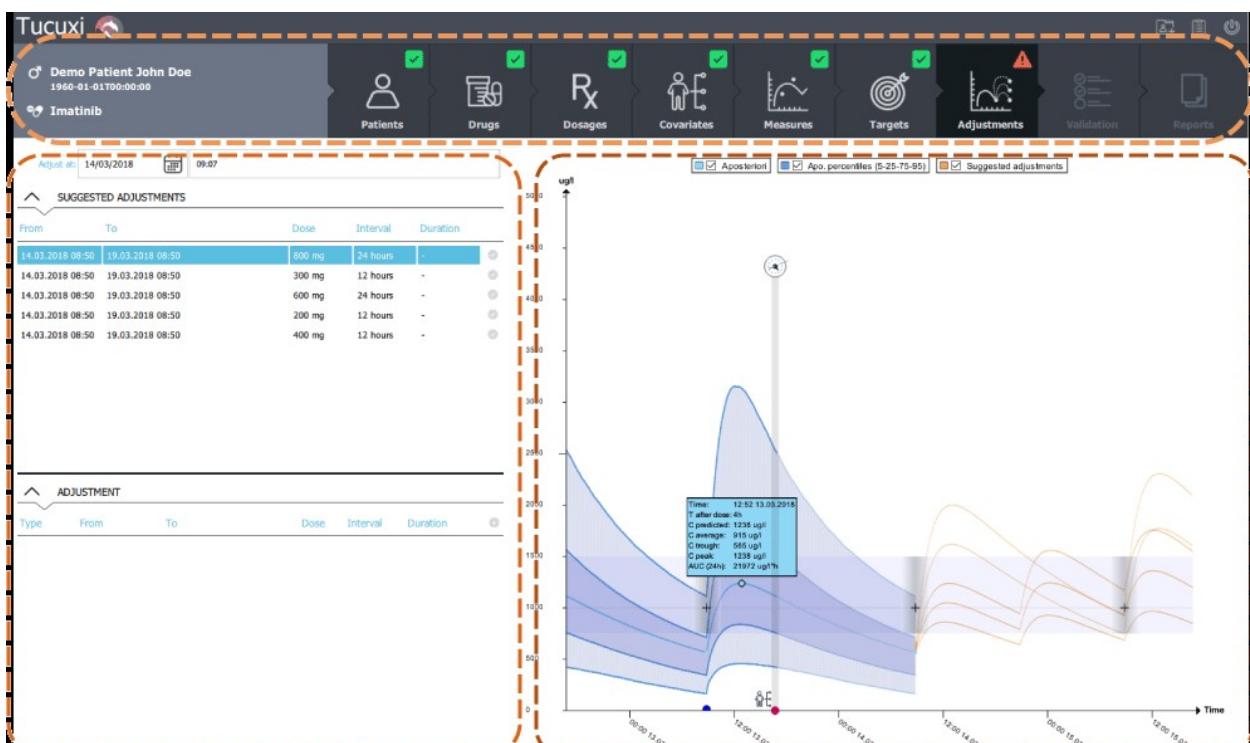
The process panel situated on the top displays every step of the treatment analysis, from the beginning on the left to the end on the right, allowing to navigate through them. The order of this flow varies slightly depending on the state of the treatment started with the patient.

Regarding the analysis of measured drug rates from a patient currently in treatment, the process is the following:

Regarding the case of a patient who has not received any doses of drugs yet, the process is the following:

The step in progress is slightly darker than the others. Each step is represented with an icon and a checkbox on the top right corner to indicate the state of the process.

	valid parameters set
	step in progress
	invalid parameters





The part below displayed in two equal sections is used to set values and show informations. On the left part, the control panel allows to set and edit parameters listed in different sections below collapsible titles. The plus symbol (1) on the top right corner of lists allows to add an element. Removing one is possible with the minus symbol (2) on the right of each row and the pen symbol (3) next to it can be used to edit the element. To set dates, an information field can be manually filled with the DD/MM/YYYY format or by choosing the date by clicking on the calendar icon (4).

Some parameters to set require to fill a window with information fields.

ID	Value	Sample date	Arrival date
01	15 ug/l	15.03.2018 09:22	15.03.2018 09:22
02	0 ug/l	15.03.2018 15:54	15.03.2018 15:54

On the right, the graph panel displays graphs and informations given the parameters set for each step. Curves are shown with percentiles values of the result for the ordered list {5, 25, 75, 95}. The 5-95 percentile area is shown lighter than the 25-75 percentile area. Clicking on the principle curve prompts an information box providing the exact details of the value of the point selected and precisions about the concentration.

Clicking on the checking box of each legend allows to remove or add curves. **Apriori** curves show the results based on a sub-group of the population with specific covariates. **Aposteriori** curves are the results of the measured drug concentration.

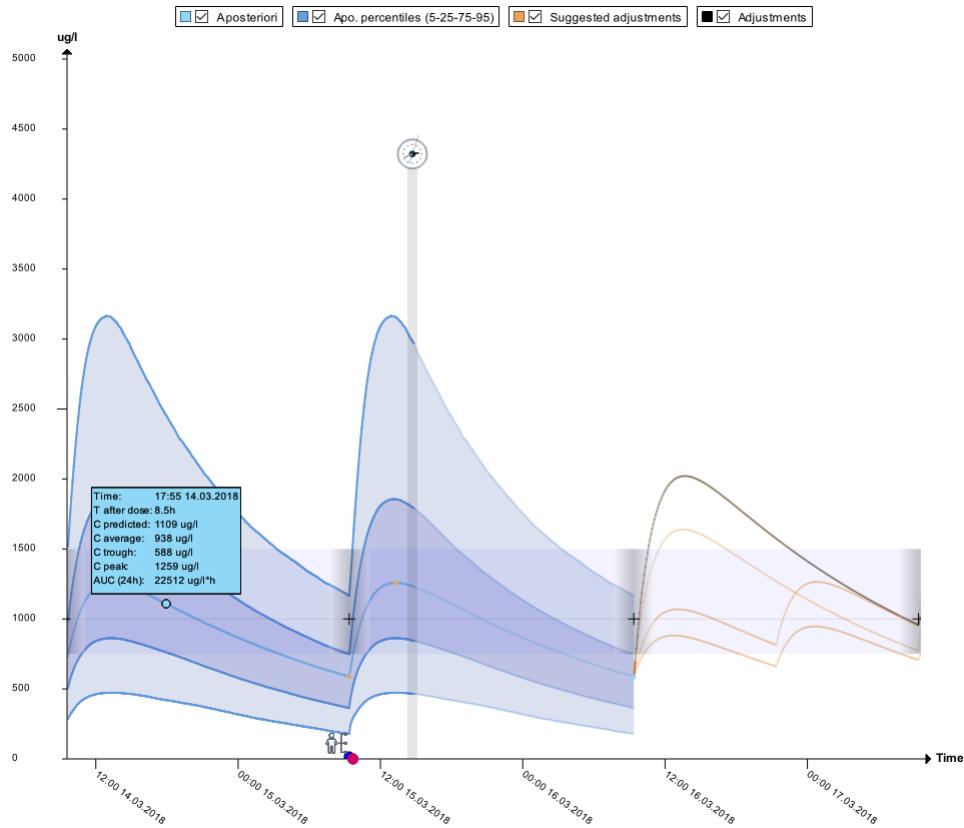
The time's scale axe is editable by scrolling anywhere on the graph area. Moving in the time's axe is possible by maintaining a selected point and moving to the right or to the left area of the graph.

A grey vertical line with a clock icon appears to indicate the current situation of the patient at the current time.

4.2.1 Graph settings

By default Tucuxi centers the graph on the end of the treatment, adjusts the time scale, and scales the Y-axis to allow all curves to fit in (percentiles and adjustments). However the user can act on different values:

- Vertical scale:
- Horizontal scale:
- **Horizontal displacement:**
 - Continuous:
 - Event-based:



4.3 1. Patients

In this first step, three sections are listed, to register or/and to display informations about the patient.

The **Patients list** displays the registered patients in a list indicating their ID, first name, last name and birth date. A window to fill with the required informations appears (? not shown in demo). Selecting a patient from the list generates automatically the patient's informations in the two sections below.

The **Patient required information** section must be completed in order to register a new patient, requiring to give the patient's first name, last name, birth date and gender.

The **Patient extra informations** allows you to add several informations such as the patient's ID, stay number and the patient's complete address.

4.4 2. Drugs

In this second step, there are three sections displaying several informations about the drugs provided to the patient for the current analysis treatment.

The **Active substance** lists the supported drugs in Tucuxi, also referenced in the “Supported drugs” chapter of this manual. For the registration of a new patient, selecting one of them is necessary to go to the next step. By choosing a drugs, its informations details are shown in two sections below and on the right panel. The **Domain** section indicates informations about the user range of the selected drug. The **Study** section quotes the source study of the selected drug.

On the right panel, more detailed informations about the drug is displayed.

ID	First Name	Last Name	Birth Date	
P001	Demo Patient John	Doe	01.01.1960	
P002	Demo Patient Jane	Doe	02.01.1960	

PATIENT REQUIRED INFORMATION

First name:	Demo Patient John	Last name:	Doe
Birth date:	01/01/1960		Gender:
			<input checked="" type="radio"/> Male <input type="radio"/> Female

PATIENT EXTRA INFORMATIONS

Identifier:	P001	Stay number:	S001
Address:	Avenue de Lausanne 1		
City:	Genève	Postcode:	1000
State:	GE	Country:	Switzerland

ACTIVE SUBSTANCE

Busulfan	Imatinib
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Imatinib

Model: ezechiel.model.linear.1comp.extra.clv
 ATC: L01XE01
 Brands: Gilevec
 Domain: Adult, (Disease: CML and GIST, Age range: 20-88 yrs, Weight range: 44-110kg, AGP plasma concentration range: 0.4-2.0 g/L)
 Study: Based on Widmer et al. Br J Clin Pharmacol 2006, validated by Gotta et al. Clin Pharmacokinet 2012
 Absorption, distribution, metabolism, and excretion
 Intake: EXTRA
 Distribution: 1 compartments
 Elimination: linear

DOMAIN

Adult, (Disease: CML and GIST, Age range: 20-88 yrs, Weight range: 44-110kg, AGP plasma concentration range: 0.4-...

STUDY

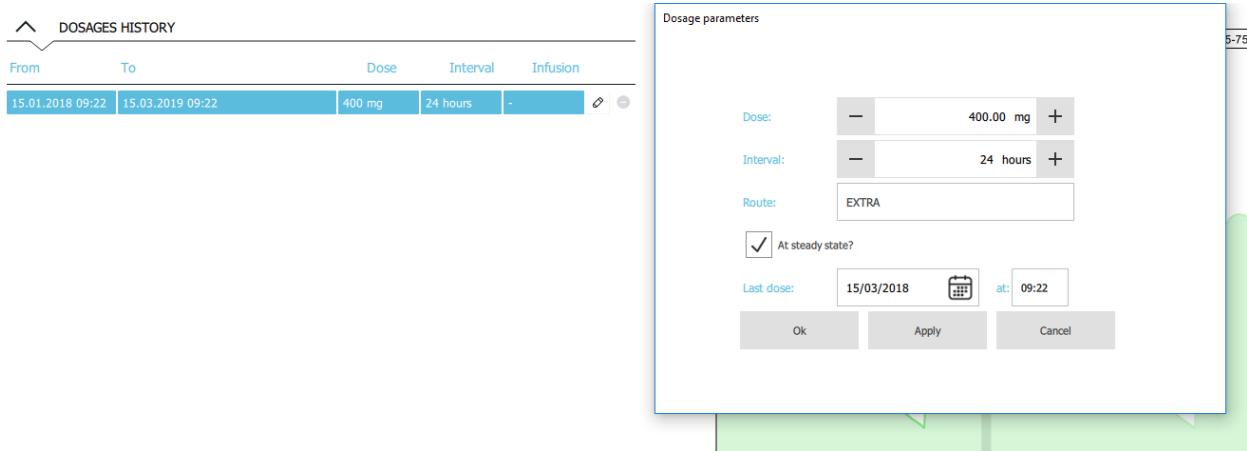
Based on Widmer et al. Br J Clin Pharmacol 2006, validated by Gotta et al. Clin Pharmacokinet 2012

4.5 3. Dosages

This step shows informations about dosages previously given to the patient.

On the control panel, the **Dosages history** section displays the list of dosages. Each row indicates the dosage of the drug and the route of drug administration.

Adding or editing a dosage prompts a parameters window with empty field to complete. Steady state constatation is included in the informations to give. Clicking on *Apply* displays the curve corresponding to the value set. Clicking on *Ok* validates the dosage.



On the graph panel, the curve corresponding to each dosage selected, applied or set is displayed and represents the prediction of drug concentration evaluated in the population.

4.6 4. Covariates

In the **Covariates** step, important variates about the patient influencing the dosage drug must be set here.

For each drug subject to the treatment analysis, different **Drug variates list** is displayed on the control panel. Every variate is indicated with the variate's type and the default and current value for the patient. Selecting a variate displays the **Patient variate history** in the section below. Each row of this list indicates the selected variate's type, the value set and the date of the setting. Adding or editing a variate prompt a different parameters window of each variate.

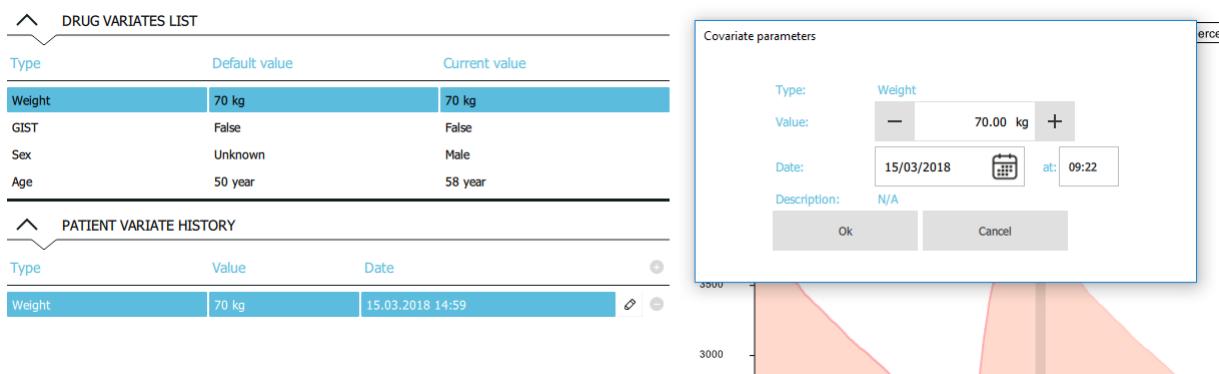
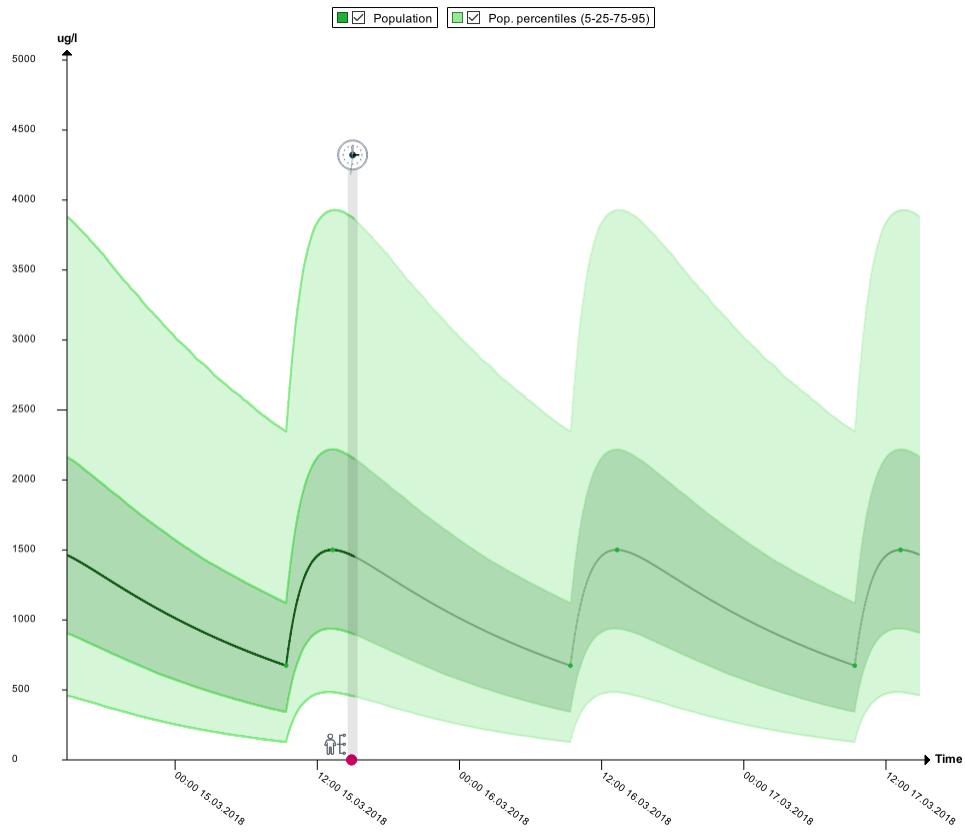
On the graph panel, the prediction curve of drug concentration is displayed and represents the result for individuals in the population given the variates set.

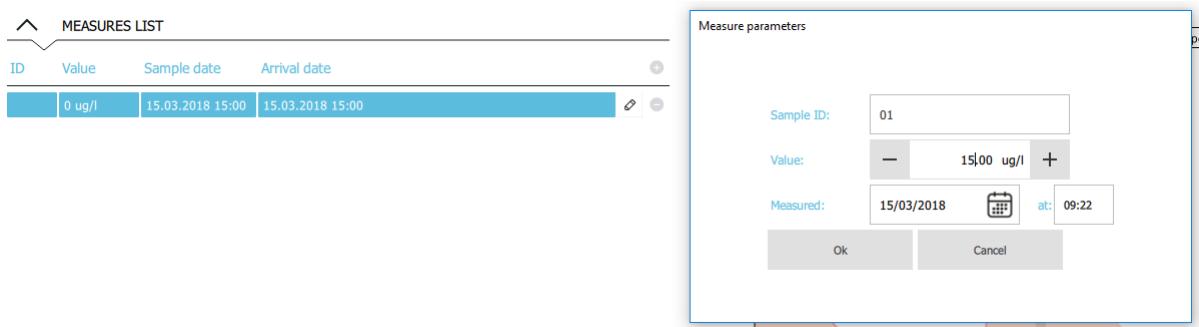
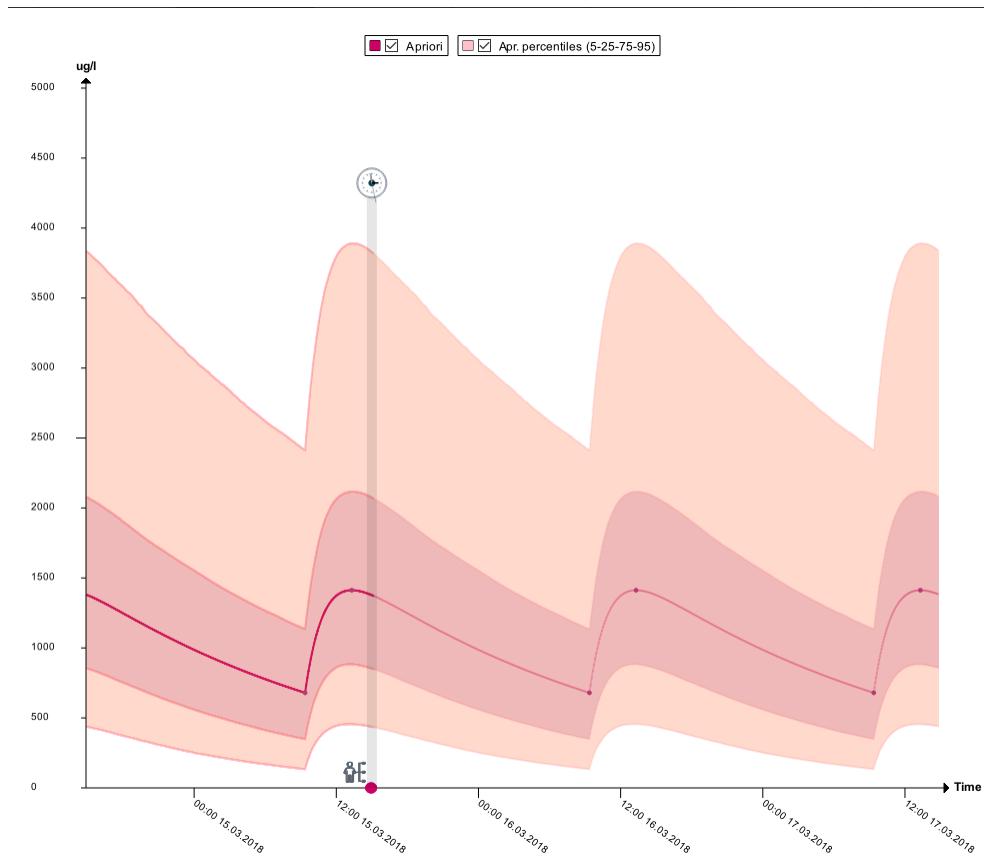
4.7 5. Measures

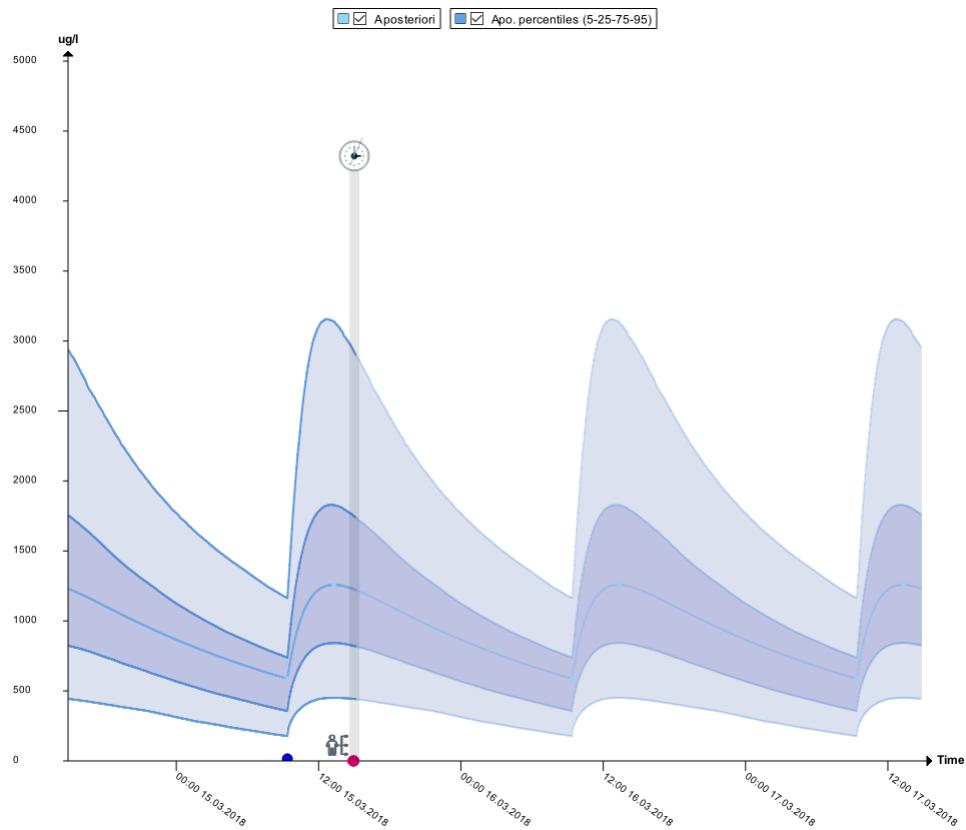
In this step, measures of the rate of drugs in the sample to analyze is listed with corresponding curves.

In the **Measures list** the previous measures done are displayed. Each measure's row indicates the ID sample, the rate value, the sampling date and the sample's date arrival. Adding or editing a measure prompt a winodw (?eng) with those datas to set.

On the graph panel, the result measured is displayed and represents the prediction curve of drug concentration of the patient. (percentil?)







4.8 6. Targets

This step concerns the target given for a patient's case depending on the informations set in previous steps.

The **Targets list** displays a target generated with the previous parameters given for the current treatment analysis. Each target is given with the target's type (residual, peak, mean or AUC), the minimum rate, the ideal rate and maximum rate for this target.

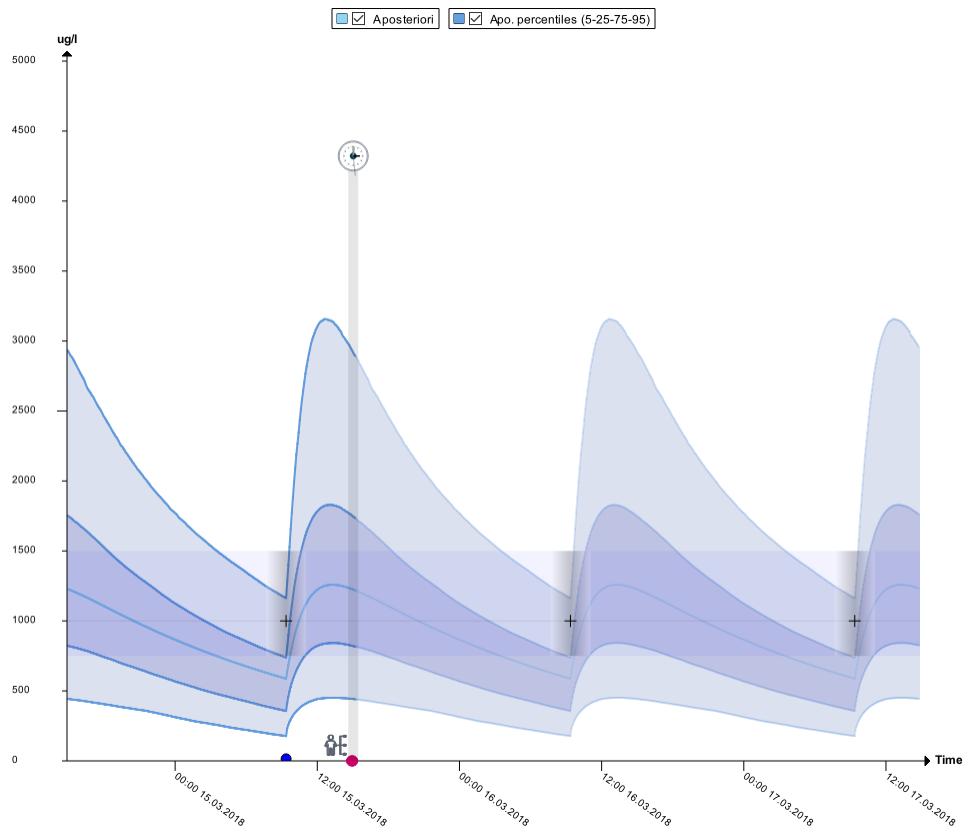
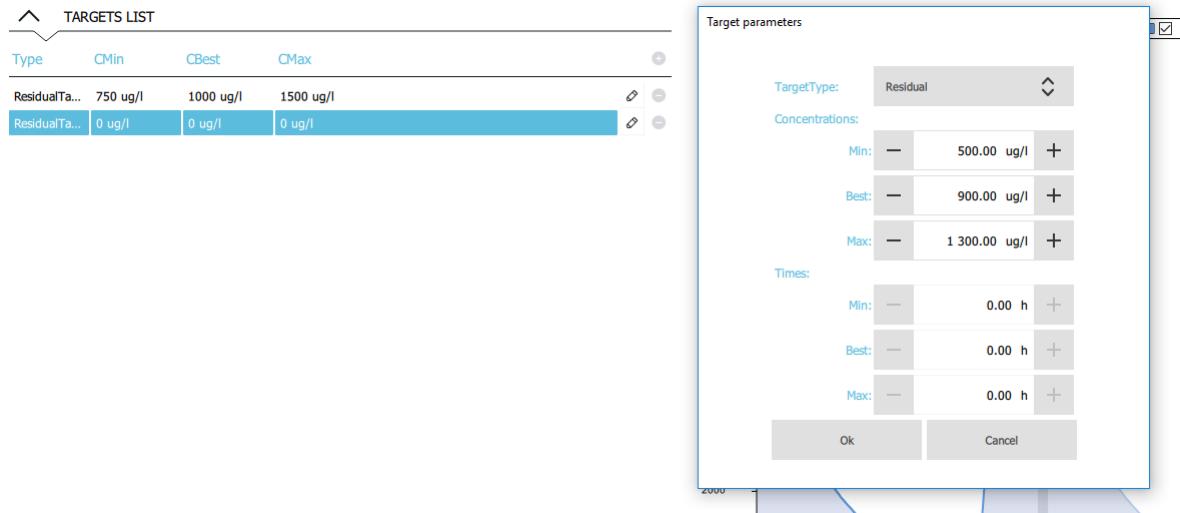
On the graph panel, the selected target range is shaded on the graph area. Black crosses indicate the ideal value (?).

4.9 7. Adjustments

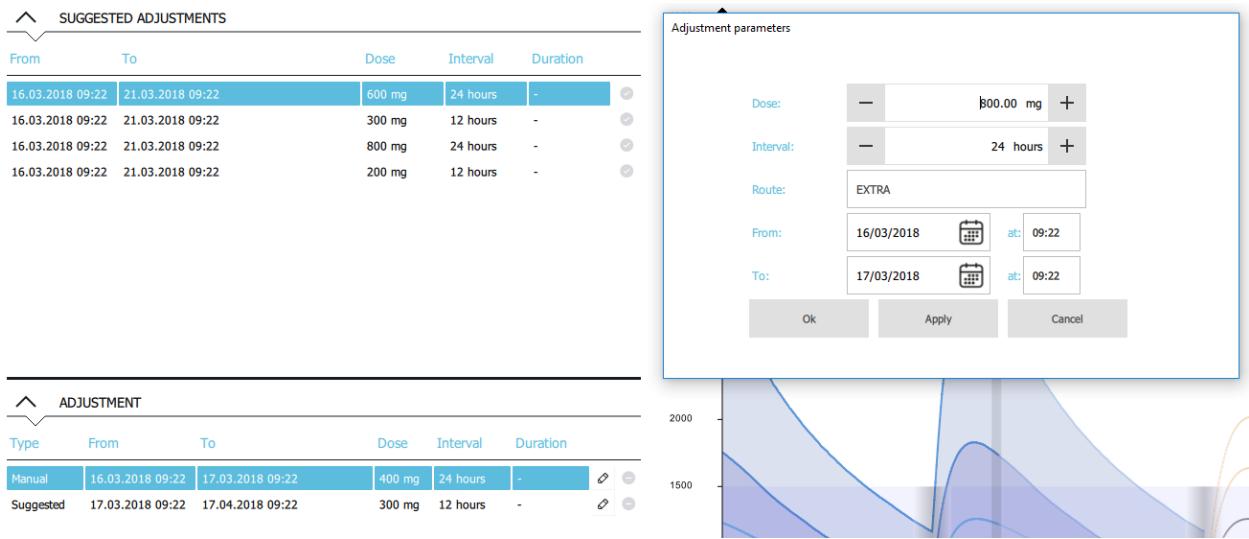
In this step, the adjusted dosage must be set.

Dosages generated with the parameters previously set are suggested in the **Suggested adjustments** section. In the section **Adjustment** below, the dosage of drugs to administrate to the patient have to be set and will be displayed here.

If a loading dose to give is necessary, a single manual dose can be chosen, by clicking on the plus symbol of the **Adjustment** section. A window appears with parameters to set (? pas de fenêtre, parce que demo?). To decrease the rate and reach the desired target, a suggested adjustment can be selected by clicking on the checked symbol on the right of the chosen dosage. The choice will be displayed on the section **Adjustment** below, after the manual adjustment set for the first dose. Those adjustments are editable, displaying a window with the parameters to set: the interval of time in which the drug should be administrated, the dose to give, in which interval of time and the duration of time in the case of an infusion. Clicking on *Apply* changes the curve displayed on the graph panel and clicking on *Ok* validates the parameters.



The date and time of the moment when the adjustment is made is shown and editable above the sections.



On the graph panel, for each suggested dosage adjustment, the expected curve of drug concentration is displayed in yellow, following the existing curve of the current treatment analysis. The curve of the selected suggestion adjustment is shown thicker and the expected curve of the loading dose of the manual adjustment set is shown in a thin black curve.

4.10 8. Validation

In this step, detailed informations are displayed with the final dosage. Comments on the treatment can be added and validated to end the analysis.

(?) In the **Parameters** section, values of parameters given the calculation model are shown.

The **Display section** allows you to specify the presence of the Measures and the Targets on the graph panel (?).

In the **Validation** section, final dosage(s) chosen during the Adjustment step are displayed. (The manually set adjustment corresponds to the first dosage shown if a loading dose was needed). The date and time of the next control can be specified. Some comments on the expectedness, suitability, prediction, remonitoring and warning can be added by filling the empty fields. Selecting *validate* ends the treatment analysis.

(?) On the graph panel, every curve generated in the previous steps are displayable.

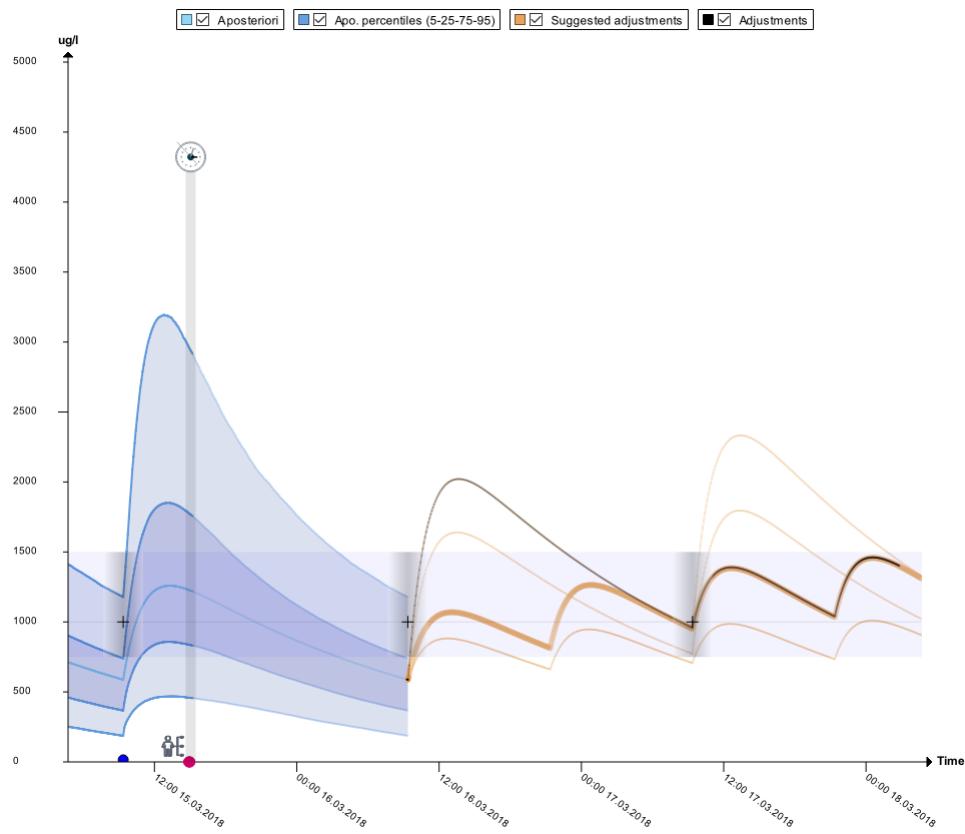
4.11 9. Reports

This last step shows the report generated for the analyzed treatment.

A section is dedicated to the comments of the treatment given in the step before in addition to the patient's current informations and variates. Informations about the sample such as the ID sample, the sampling date and the measured rate are shown. The graph generated during the treatment analysis is also displayed, illustrating the previous and futur concentration profile. The final dosage proposed and the date of the next control is shown on the bottom of the report.

A pdf can be generated by clicking on the button below the report.

On the graph panel, every curve showing the informations about the treatment analyzed is displayed.



PARAMETERS

Population: CL = 14.300 F = 1.000 Ka = 0.609 V = 347.000

Apriori: CL = 15.666 F = 1.000 Ka = 0.609 V = 393.200

Aposteriori: CL = 17.768 F = 1.000 Ka = 0.609 V = 428.719

DISPLAY SELECTION

Measures Targets

VALIDATION

Posology From 16.03.2018 at 09:22 : 800mg every 24 hours (extravascular)

From 17.03.2018 at 09:22 : 300mg every 12 hours (extravascular)

Next control: 17/04/2018



09:22

Expectedness: Please fill in

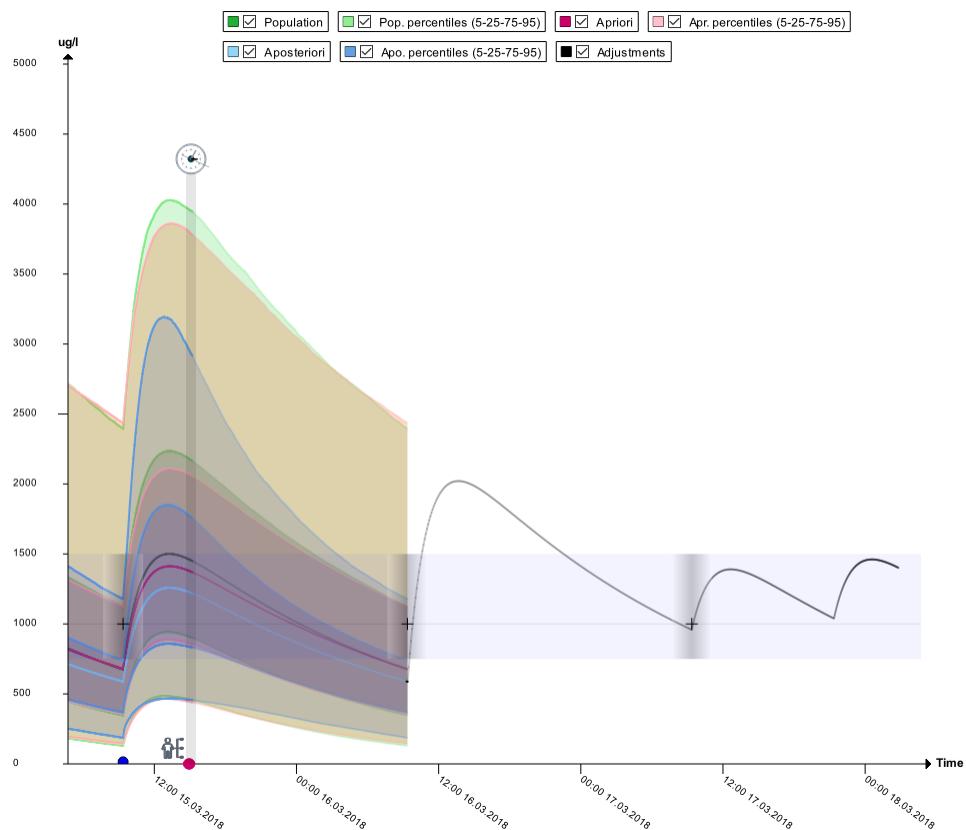
Suitability: Please fill in

Prediction: Please fill in

Remonitoring: Please fill in

Warning: Please fill in

Validate



 COOK COUNTY GENERAL HOSPITAL
Clinical pharmacology division
Biomedicine service

Drug laboratory
Dr. Mark Greene, laboratory manager
Tel. +41 (0) 11 222 3333
Fax +41 (0) 11 222 3334

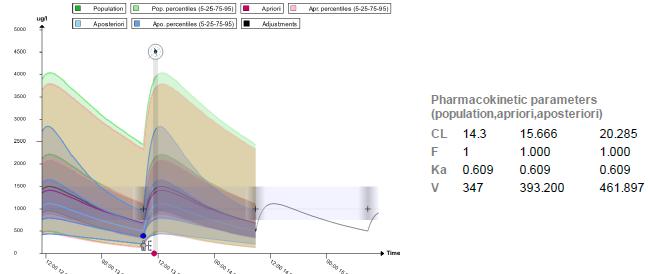
Therapeutic Drug Monitoring Unit
Dr. John Carter, head-physician
Tel. +41 (0) 11 222 3335
Tel. +41 (0) 11 222 3336

Therapeutic Drug Monitoring: imatinib

Patient:	Demo Patient John Doe	ID:	P001	Date of birth:	1960-01-01
Weight:	70 kg	GIST:	0	Sex:	Female
Expectedness:	Hi				Age:
Suitability:	Br				58 year
Prediction:	e				
Remonitoring:	f				
Warning:	g				

Sample from:	2018-03-13 08:50	ID:	Result:	400ug/l
Last dose:	2018-03-13 08:50		Dosage:	400mg

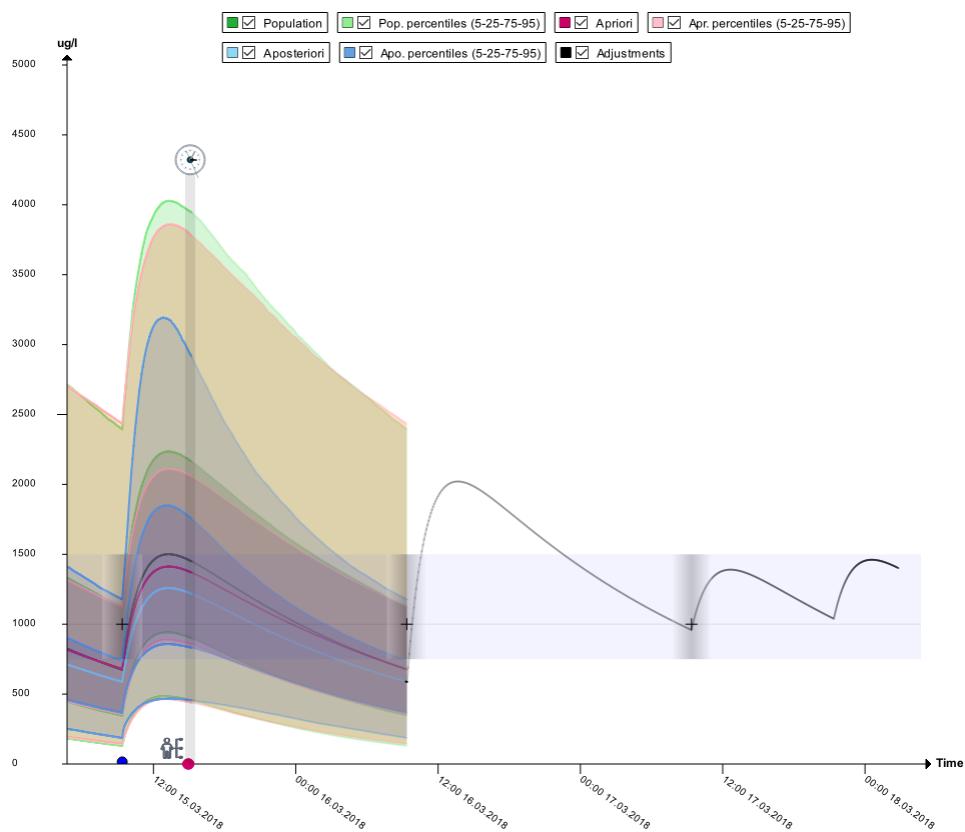
Predictions



Pharmacokinetic parameters (population,apriori,aposteriori)

CL	14.3	15.666	20.285
F	1	1.000	1.000
Ka	0.609	0.609	0.609
V	347	393.200	461.897

Dosage adjustment proposed	Date:	2018-03-13
Dosage:	From 14.03.2018 at 08:50 : 400mg every 24 hours (extravascular)	
	From 15.03.2018 at 08:50 : 300mg every 12 hours (extravascular)	
Next control:	15.04.2018 08:50	



5

Reference Manual

6

Supported Drugs

Indices and tables

- genindex
- modindex
- search