

## Supplementary material A: Mathematical methodology

### Model formulation

The *Cancitis model* consists of the differential equations:

$$\dot{x}_0 = (r_x \phi_x(x_0, y_0) s - d_{x_0} - a_x) x_0 \quad (1a)$$

$$\dot{x}_1 = a_x A_x x_0 - d_{x_1} x_1 \quad (1b)$$

$$\dot{y}_0 = \left( r_y \phi_y(x_0, y_0) s - \hat{d}_{y_0} - \tilde{d}_{y_0} y_0 - a_y \right) y_0 \quad (1c)$$

$$\dot{y}_1 = a_y A_y y_0 - d_{y_1} y_1 \quad (1d)$$

$$\dot{a} = d_{x_0} x_0 + d_{x_1} x_1 + \left( \hat{d}_{y_0} + \tilde{d}_{y_0} y_0 \right) y_0 + d_{y_1} y_1 - e_a a s \quad (1e)$$

$$\dot{s} = r_s a - e_s s + I \quad (1f)$$

with

$$\phi_x(x_0, y_0) = \frac{1}{1 + c_{xx} x_0 + c_{xy} y_0} \quad (2)$$

$$\phi_y(x_0, y_0) = \frac{1}{1 + c_{yx} x_0 + c_{yy} y_0} \quad (3)$$

where  $x_0$  denotes the healthy stem- and progenitor-cells,  $y_0$  denotes the leukemic stem- and progenitor-cells,  $x_1$  the healthy mature cells,  $y_1$  the leukemic mature cells,  $a$  the debris of dead cells and  $s$  is an abstract notion of the immune system load. The default parameters values used are shown in table 1.

$r_x$	$8.7 \cdot 10^{-4}$	$r_y$	$15 \cdot 10^{-4}$	$a_x$	$1.1 \cdot 10^{-5}$	$a_y$	$0.52 \cdot 10^{-5}$
$d_{x_0}$	$2 \cdot 10^{-3}$	$d_{y_0}$	$2 \cdot 10^{-3}$	$\hat{d}_{y_0}$	$2 \cdot 10^{-9}$	$\hat{d}_{y_0}$	$2 \cdot 10^{-3}$
$A_x$	$4.7 \cdot 10^9$	$A_y$	$4.7 \cdot 10^9$	$d_{x_1}$	$1.29 \cdot 10^{-2}$	$d_{y_1}$	$1.29 \cdot 10^{-2}$
$c_{xx}$	$5.6 \cdot 10^{-5}$	$c_{xy}$	$5.4 \cdot 10^{-5}$	$c_{yx}$	$5.2 \cdot 10^{-5}$	$c_{yy}$	$5.0 \cdot 10^{-5}$
$e_a$	$2 \cdot 10^5$	$e_s$	2	$r_s$	$3 \cdot 10^{-4}$	$I$	7

Table 1: Default values for the parameters of the Cancitis model.

A reduced model is proposed and analysed by Ottesen et al. (2019). The model reduction is based on quasi-steady-state approximations of  $\dot{x}_1$ ,  $\dot{y}_1$ ,  $\dot{a}$  and  $\dot{s}$ . The quasi-steady-state approximations imply the following algebraic expression:

$$x_1 = \frac{a_x A_x}{d_{x_1}} x_0 \quad (4a)$$

$$y_1 = \frac{a_y A_y}{d_{y_1}} y_0 \quad (4b)$$

$$a = \frac{1}{2} \sqrt{\left( \frac{I}{r_s} \right)^2 + 4 \frac{e_s \kappa}{e_a r_s} - \frac{I}{2 r_s}} \quad (4c)$$

$$s = \frac{r_s}{e_s} a + \frac{I}{e_s} \quad (4d)$$

where  $\kappa = d_{x_0} x_0 + d_{x_1} x_1 + (\hat{d}_{y_0} + \tilde{d}_{y_0}) y_0 + d_{y_1} y_1$ . The two-dimensional system is then simply:

$$\dot{x}_0 = (r_x \phi_x(x_0, y_0) s - d_{x_0} - a_x) x_0 \quad (5a)$$

$$\dot{y}_0 = \left( r_y \phi_y(x_0, y_0) s - \hat{d}_{y_0} - \tilde{d}_{y_0} y_0 - a_y \right) y_0 \quad (5b)$$

Cell-counts are interpreted from the model as:

$$\text{Leukocytes} = K_{\text{leukocytes}}(x_1 + y_1) \quad (6a)$$

$$\text{Thrombocytes} = K_{\text{thrombocytes}}(x_1 + y_1) \quad (6b)$$

## Dose-dependent perturbation of model parameters

Some differences in dosing and timing of IFN treatment occurred in the DALIAH trial. Dosing information was approximated as the average daily dose, but to have gradual changes in IFN-perturbed parameters, we made use of a simple pharmakokinetic model of IFN. Absorption and clearance of IFN was modelled to occur with the same rate,  $\tau$ , independently of the current dose. The IFN blood-concentration can hence be described by:

$$\dot{B} = \frac{1}{\tau} (D(t) - B(t)) \quad (7)$$

where  $D(t)$  is the dose at time  $t$  and  $B(t)$  is the blood concentration at the given time. Note that  $D(t)$  is a stepsize constant function describing the average daily dose. Considering an interval  $t \in [t_0, t_1]$  where  $D(t)$  is constant,  $D(t) = D_0$ , the differential equation (7) has solution:

$$B(t) = D_0 - (D_0 - B(t_0)) e^{-t/\tau} \quad (8)$$

for  $t \in [t_0, t_1]$ . This allowed for a very simple estimate of the blood concentration level with smooth transitions from one level of treatment to another.

The parameter  $\hat{d}_{y_0}$  was modelled to increase with the current blood-concentration of IFN. This was done by defining a function  $\hat{d}_{y_0}(\rho, t)$  such that:

$$\overline{\hat{d}_{y_0}}(\rho, t) = (1 + \rho B(t)) \hat{d}_{y_0} \quad (9)$$

where  $B(t)$  is the time-dependent blood-level concentration of IFN and  $\rho$  is a parameter describing the strength of the patient-specific response to IFN treatment. Hence, a large  $\rho$  corresponds to a significant increase to  $\hat{d}_{y_0}$  during treatment, while a low  $\rho$  signifies a low response. To ensure positive parameters, only positive values of  $\rho$  were considered.

## Fitting procedure

The *JAK2V617F* allele burden was interpreted in the model as  $C(t) = \frac{y_1(t)}{x_1(t)+y_1(t)}$ , i.e. as the contribution of leukemic mature cells to the sum of mature cells. Hence, solutions of equations (5) together with calculation of  $x_1$  and  $y_1$  from equations (4) can be used to determine a model estimate of the *JAK2V617F* allele burden.

The model was simulated numerically in MATLAB using the function `ode15s`. One healthy stem cell,  $x_0$  was removed and a leukemic stem cell  $y_0$  was added at time 0. Due to the default parameters used, the system approaches a leukemic steady-state asymptotically. The *JAK2V617F* allele burden is initially close to 0 and approaches 1 as time increases.

The development of MPN before diagnosis was assumed to be equal for all patients and hence that the untreated disease development to be the same for the population. The initial baseline measurement of the *JAK2V617F* allele burden at diagnosis was used to determine where on the common disease development curve the patient were before treatment initiation. Hence data and model were shifted in time such that baseline *JAK2V617F* coincides with the model. Simulations of treatment-response used the model variables at the corresponding time as initial conditions.

The model was simulated for each patient over the time-period where data for the given patient was available. By separately modelling the blood-concentration of IFN as described above, and simulating a dose-dependent perturbation of  $\hat{d}_{y_0}$  as shown in equation (9), the model could be simulated for different values of  $\rho$ , yielding different responses and developments of the *JAK2V617F* for the simulated time-period.

Model error was determined by the difference between the measurements of the *JAK2V617F* allele burden and the model estimate at the same time-points. Note that the baseline our methodology forces the model to be in agreement with baseline measurement. The value of  $\rho$  found to (locally) minimize the sum of squared errors was found using the MATLAB function `fminsearch`.

## Cell-count measurements

The sum of mature cells in the model was assumed to correlate with both the cell-counts of thrombocytes and of leukocytes, see equations (6). As fluctuations between cell-lines were expected, and indeed observed in data, a complete correlation with both cell-counts cannot be expected for all measurements.

By assuming a linear scaling, we were able to determine two scaling-parameters,  $K_{leukocytes}$  and  $K_{thrombocytes}$ , that minimized the sum of squares difference between cell-count data and the sum of  $x_1(t)$  and  $y_1(tx)$  the *JAK2V617F*-error minimizing fits described above. These scaling parameters then describe the proportion of mature cells in the model which can be attributed to the given cell-line; thrombocytes or leukocytes.

As some significant differences were observed between thrombocytes and leukocytes (e.g. one patient had increasing thrombocyte-counts but decreasing leukocytes counts over the study period), such linear scaling of

cell counts provides a rough estimate of the general level of mature blood-cells, and cannot be expected to be in perfect agreement with data. However, for a subset of patients, these ad-hoc blood-data fits were found to agree well with both *JAK2V617F* data and blood-cell data simultaneously even though the model was only optimised for agreement with *JAK2V617F* data, see supplementary material C.

In summary, a single parameter,  $\hat{d}_{y_0}$  was modelled to increase linearly for increasing IFN-dose. An error-minimizing fitting procedure of the *JAK2V617F* allele burden identified a patient-specific response-parameter describing the strength of the perturbation to  $\hat{d}_{y_0}$ . A subsequent fit of the resulting model estimate of mature blood-cells counts to the thrombocyte and leukocyte counts found excellent agreement between the response to IFN in data and in the model for most patients. Hence a mechanistic interpretation as IFN resulting in an dose-dependent increase of malignant stem-cell clearing ( $\hat{d}_{y_0}$ ) appears as (part of) a plausible explanation for the treatment-responses observed in patient data.

## References

- Ottesen, J. T., Pedersen, R. K., Sajid, Z., Gudmand-Hoeyer, J., Bangsgaard, K. O., Skov, V., Kjær, L., Knudsen, T. A., Pallisgaard, N., Hasselbalch, H. C., and Andersen, M. (2019). Bridging blood cancers and inflammation: The reduced Cancitis model. *Journal of Theoretical Biology*, 465:90–108.

## Supplementary material B: Fits to *JAK2V617F* data

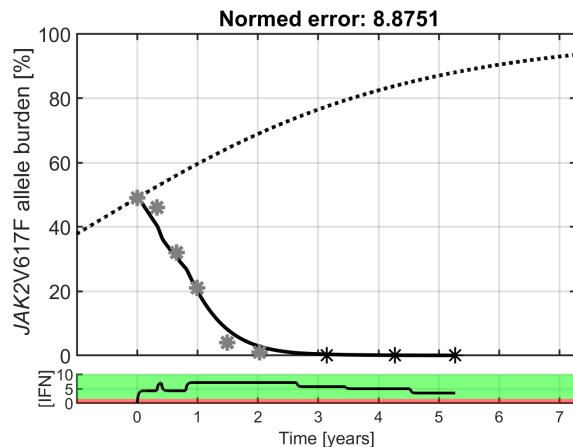
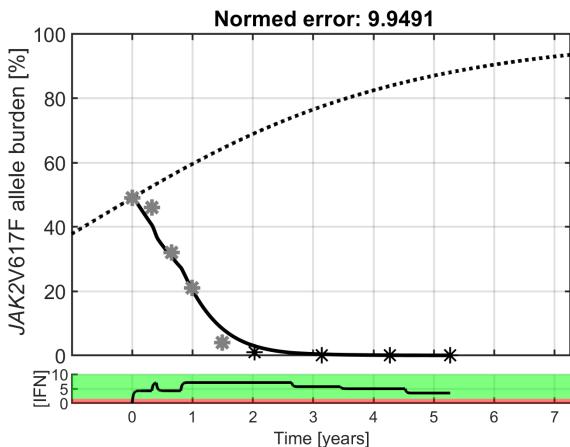
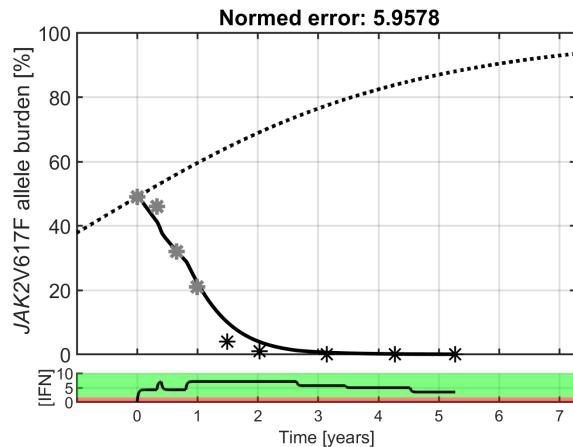
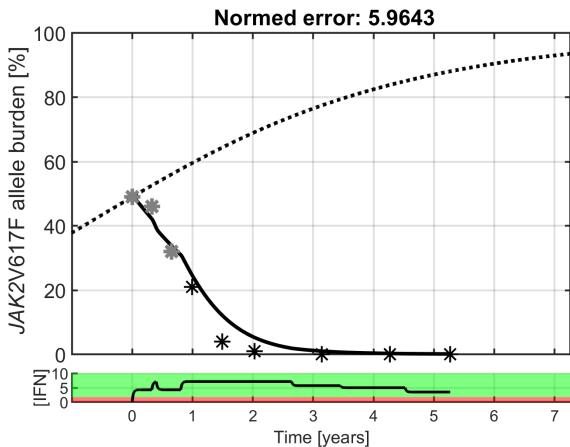
Below we show fits of the Cancitis model to all available data for the *JAK2V617F* allele burden. In the fits, the PD-effect of the IFN was modelled to increase the LSC death rate, dependent on the current blood concentration of IFN, modelled by a simple PK model as described in the main text.

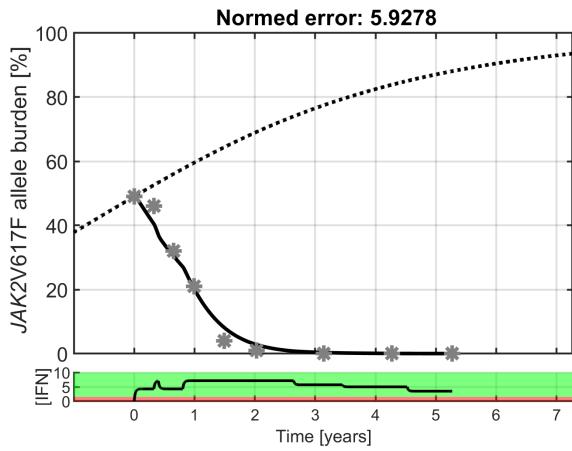
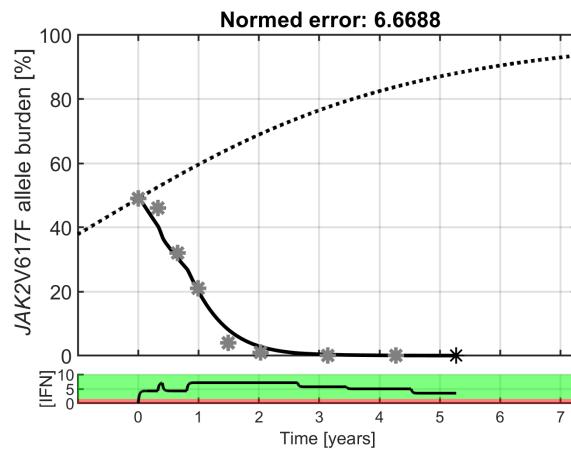
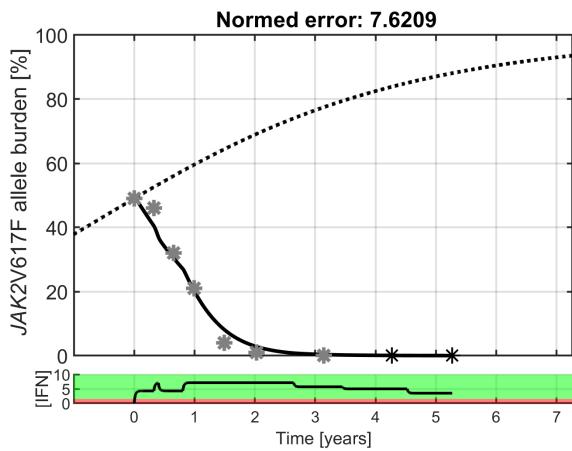
The top panel shows patient-data and the model disease burden. The dotted black curves shows disease development, assumed to be the same for all patients. Baseline *JAK2V617F* is shifted in time to coincide with this curve. Grey \* signify data-points used for the fitting procedure, while black \* signify later data-points not used for the procedure, shown only for comparison and evaluation of the model fit. The full black line shows the best fit to the given data, defined as the fit that minimizes the sum of squared distance between the used data-points and the model at the given time-points, see the supplementary describing the mathematical methods. For time after the last data-points used for fitting, the actual future dosing information was used.

The bottom panel shows the PK-modelling of the blood-concentration of IFN as a black curve. The background color signifies the long-term state that the system will move toward: For doses where the background is green, the model implies that long-term the healthy state will be approached, while the red background shows doses that will approach full-blown disease. The unit of the dose is the average daily dose of IFN in  $\mu\text{g}$ . No distinction was made between *Peginterferon- $\alpha$ -2a* (*Pegasys*) and *Peginterferon- $\alpha$ -2b* (*PegIntron*)

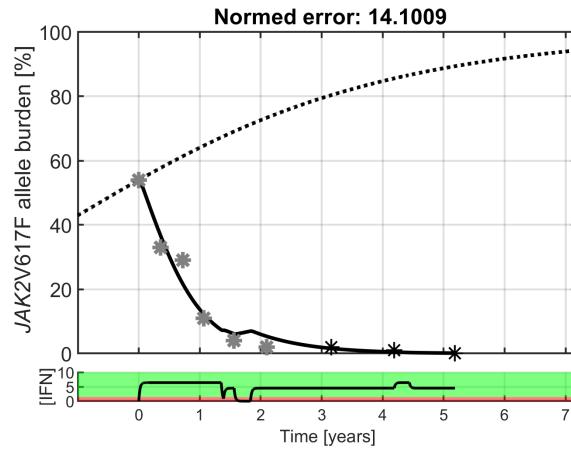
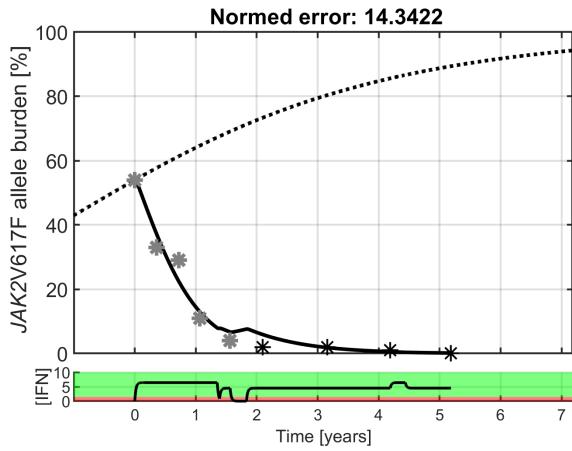
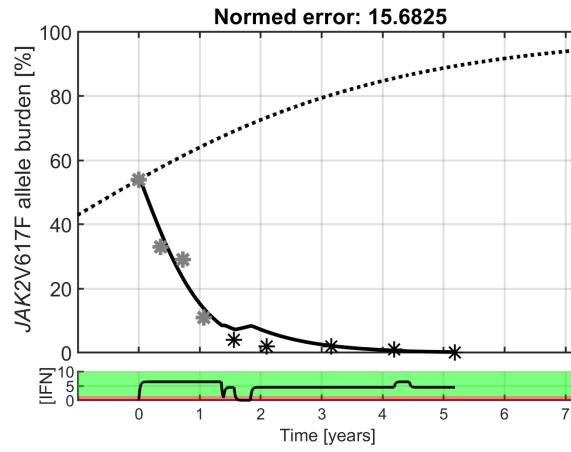
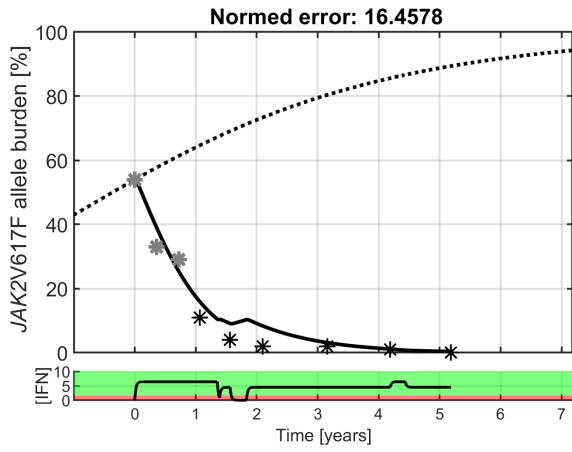
At the top of all figures, a goodness-of-fit-metric of the best fit is shown, defined as the sum of squared errors, divided by the number of points used in the fit. A low number signifies a good fit. Only the error of points used (the grey points) were included in the error estimate.

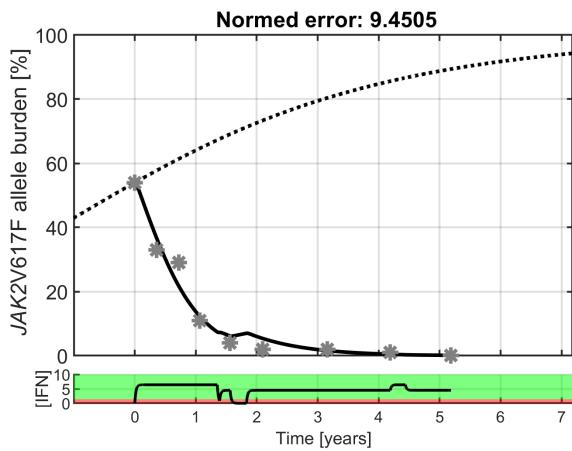
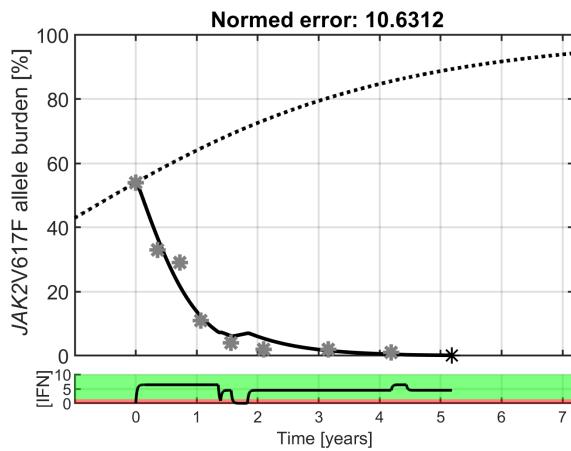
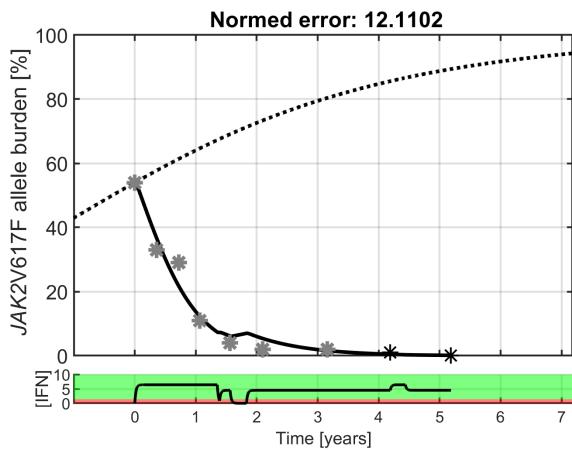
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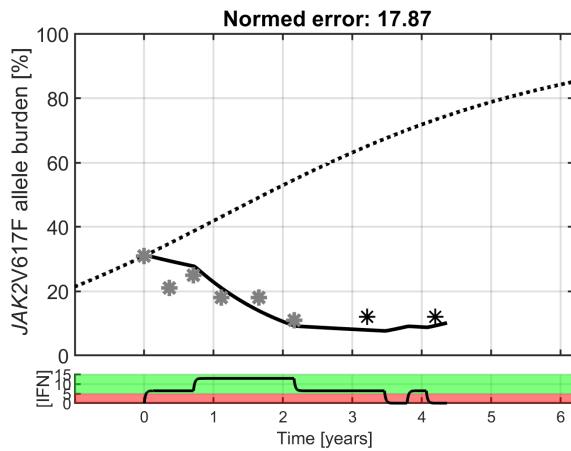
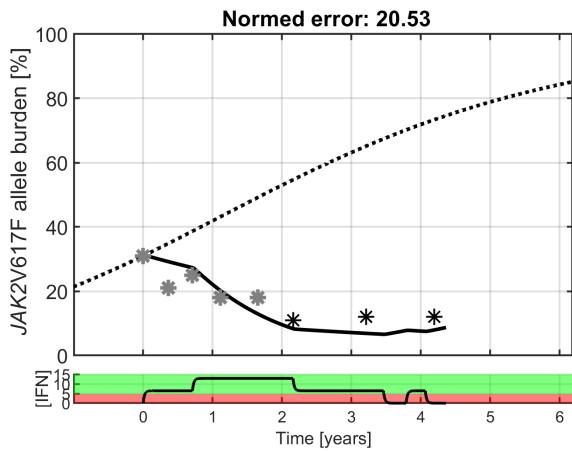
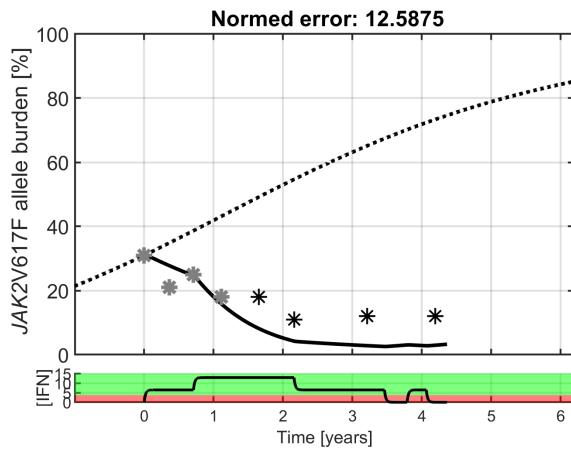
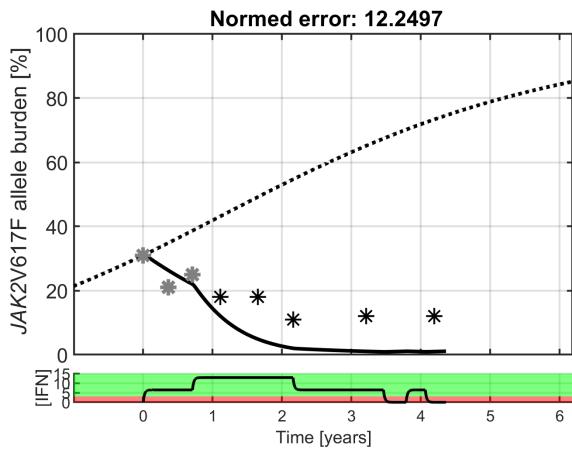


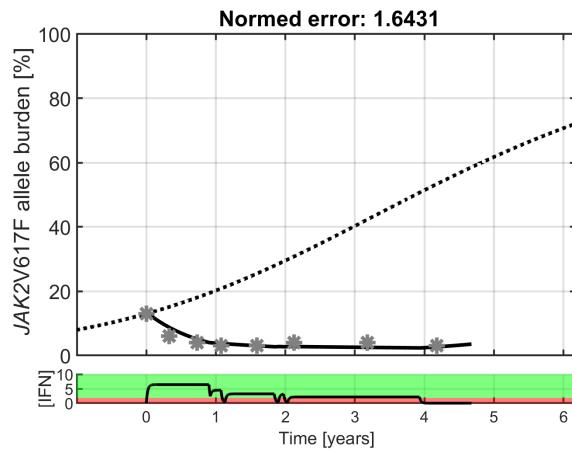
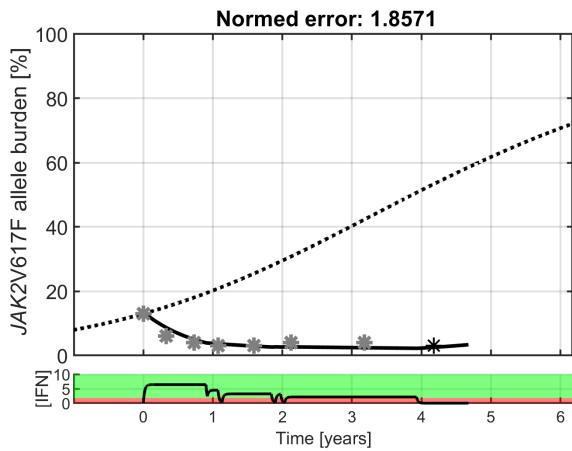
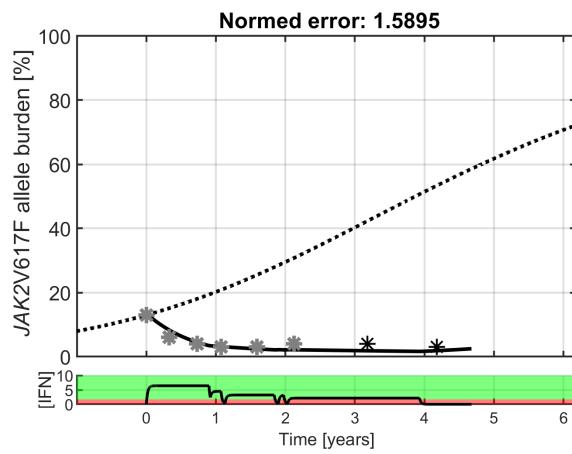
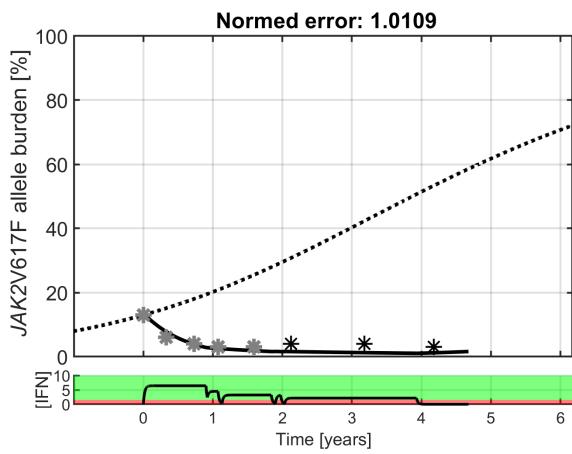
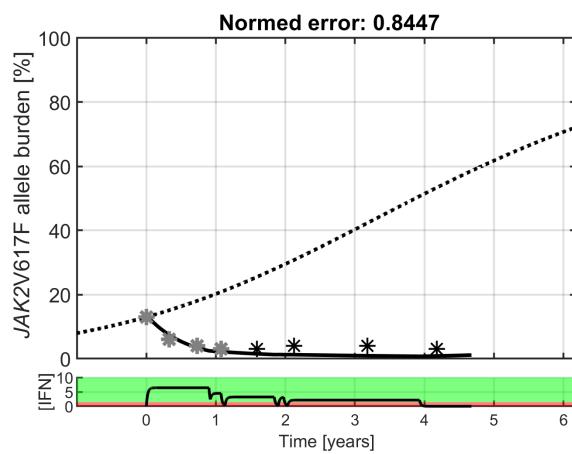
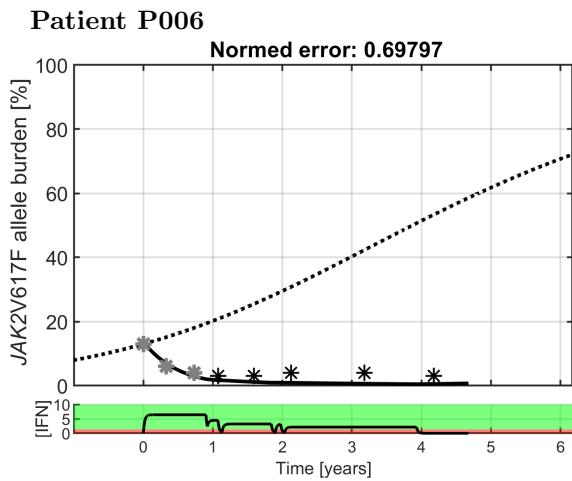
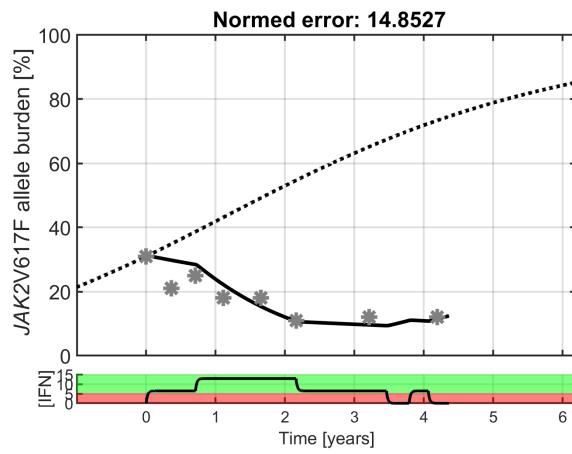
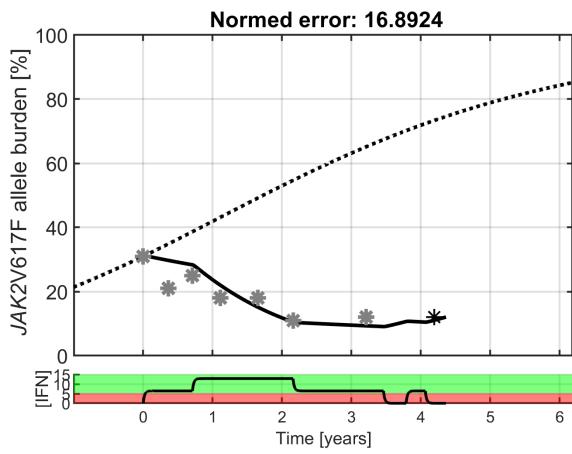
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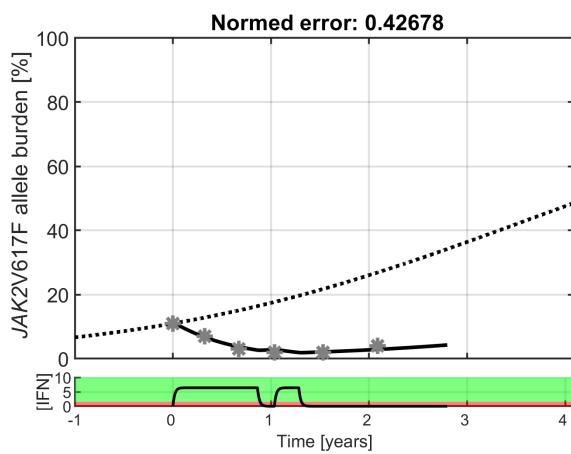
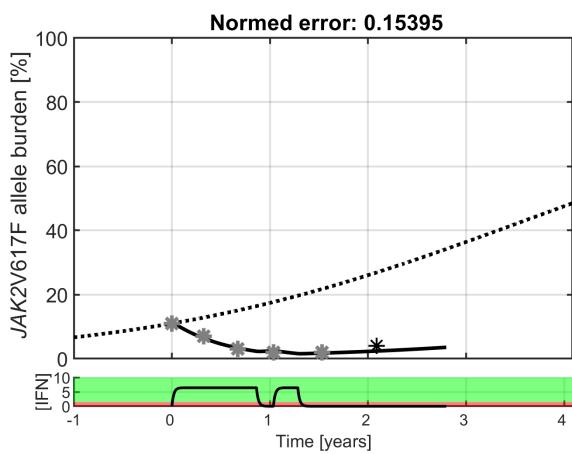
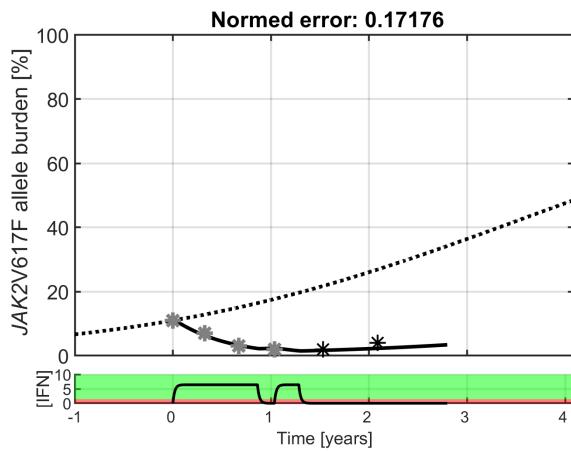
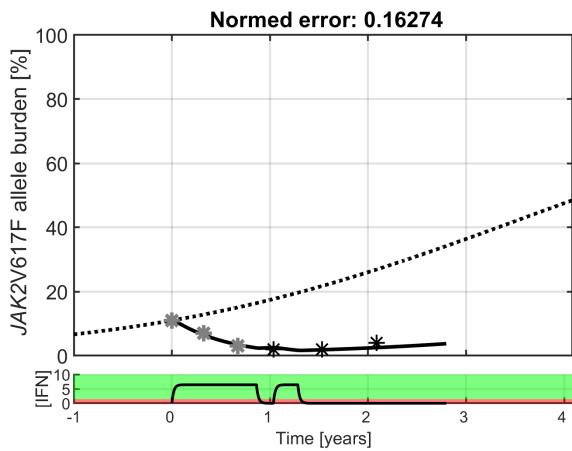


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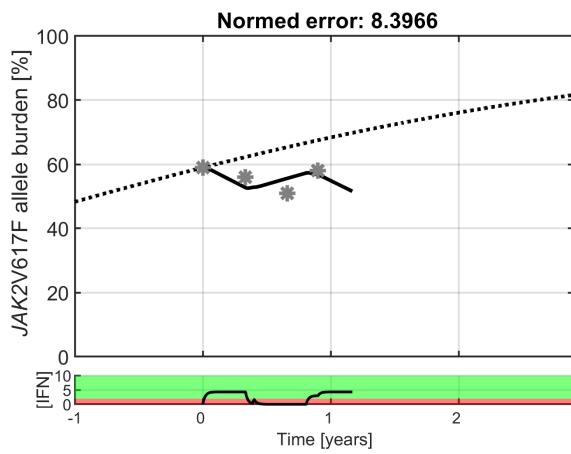
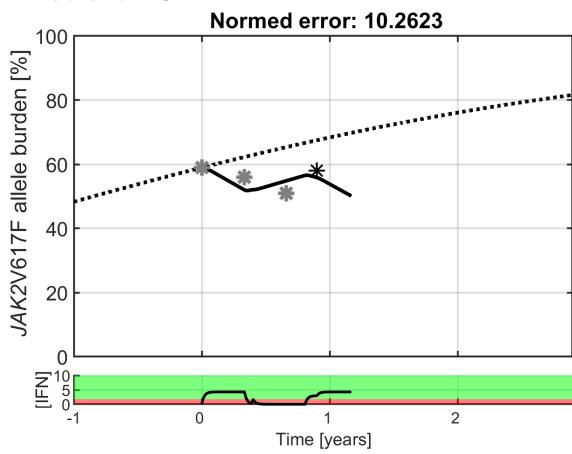




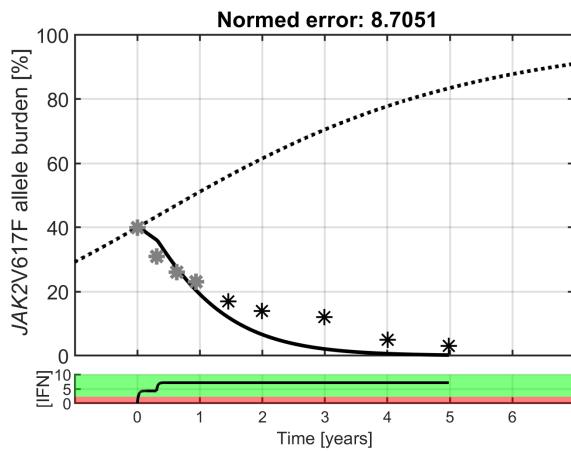
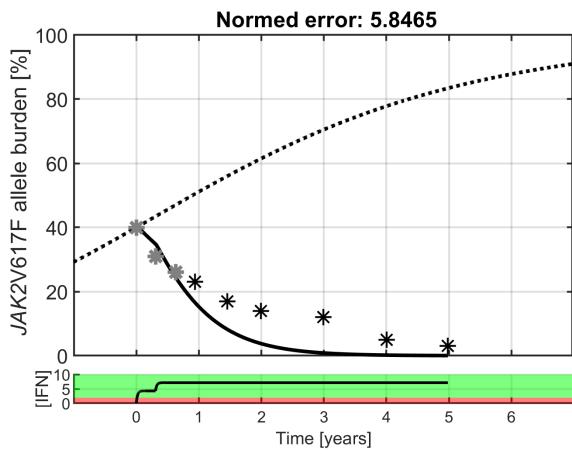
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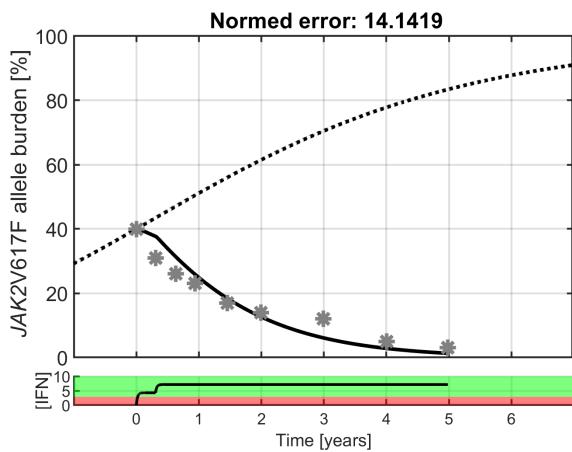
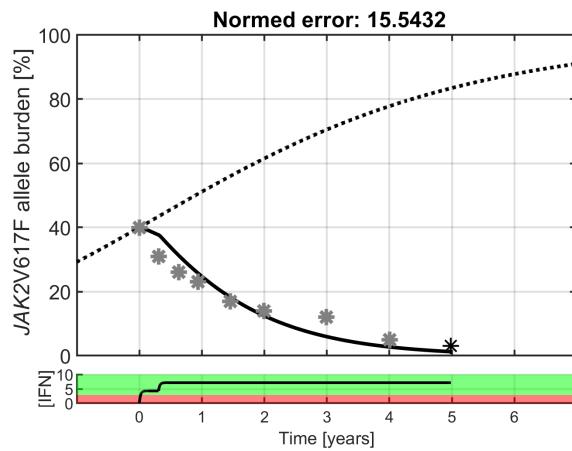
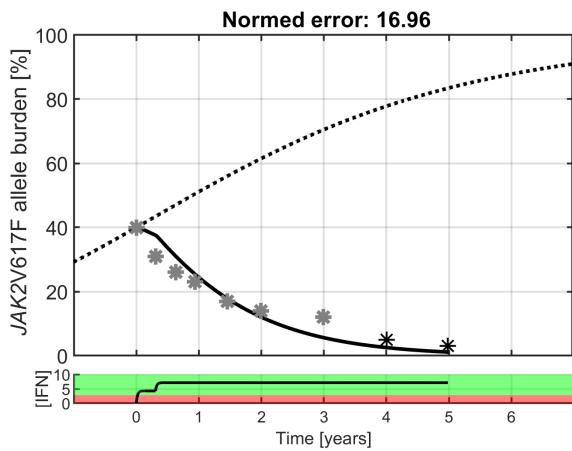
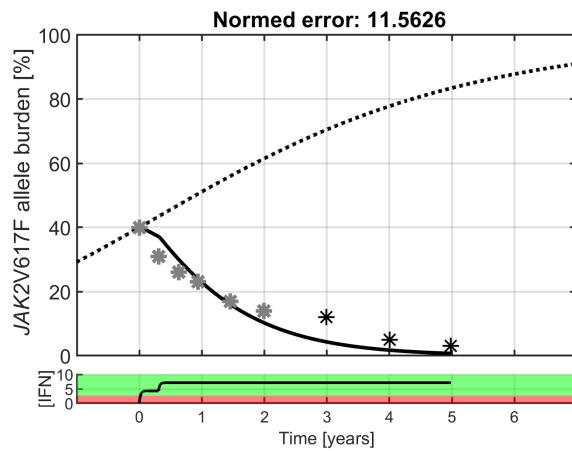
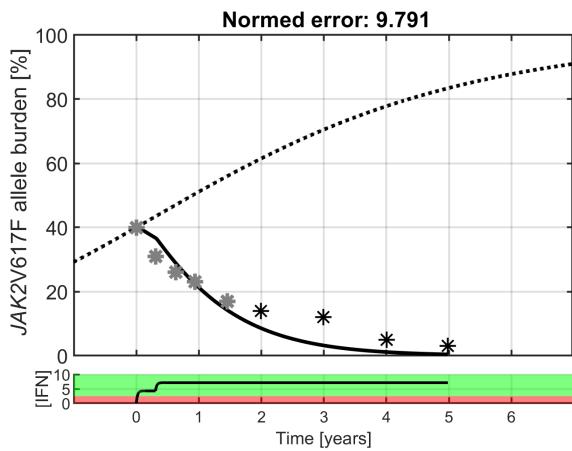


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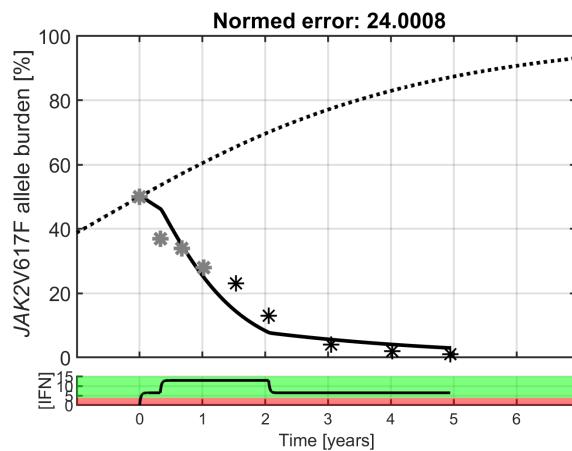
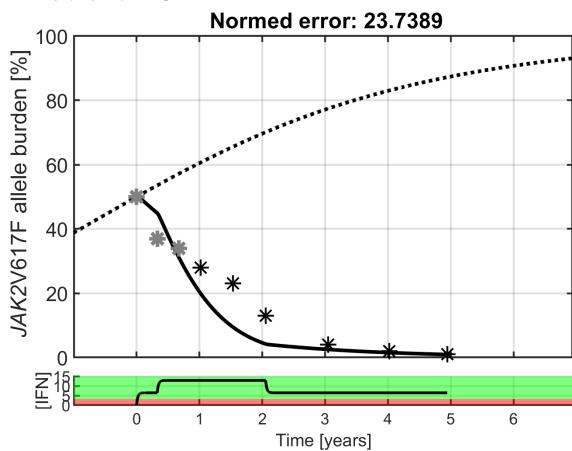


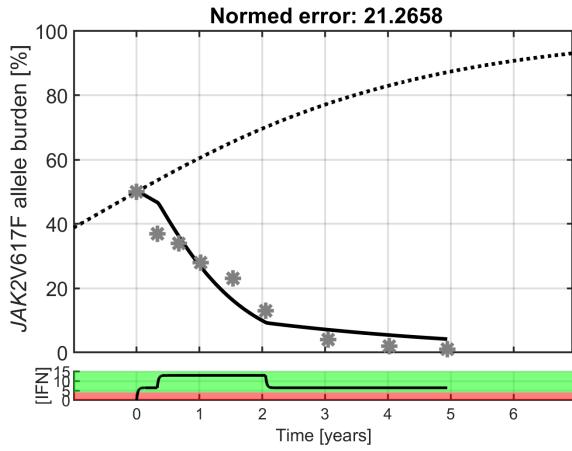
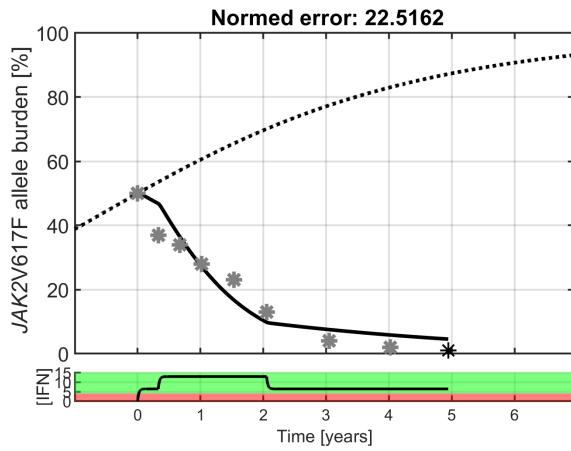
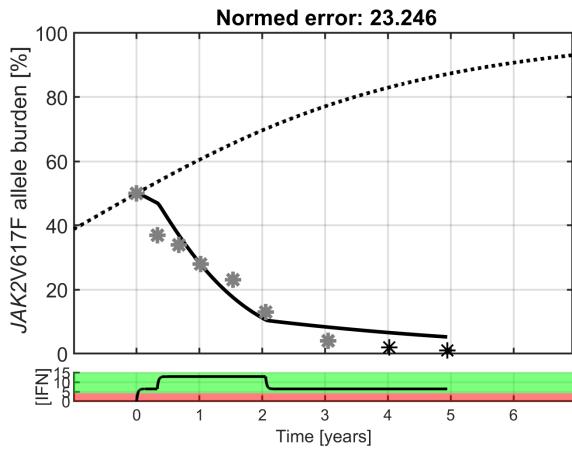
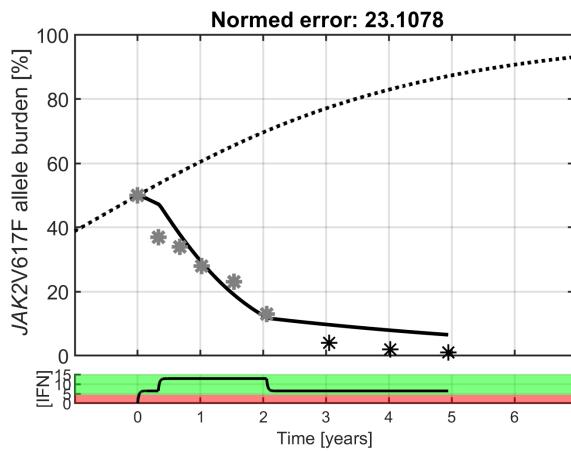
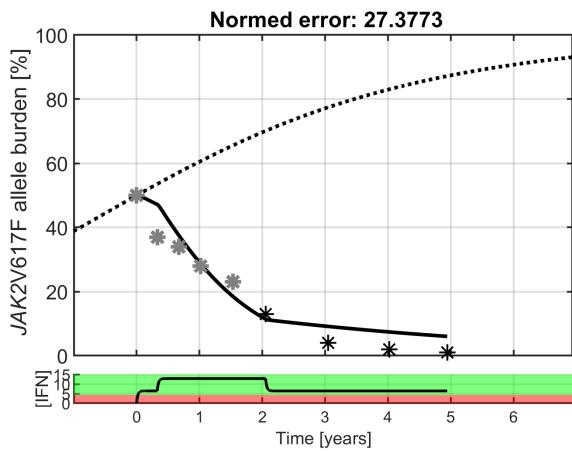
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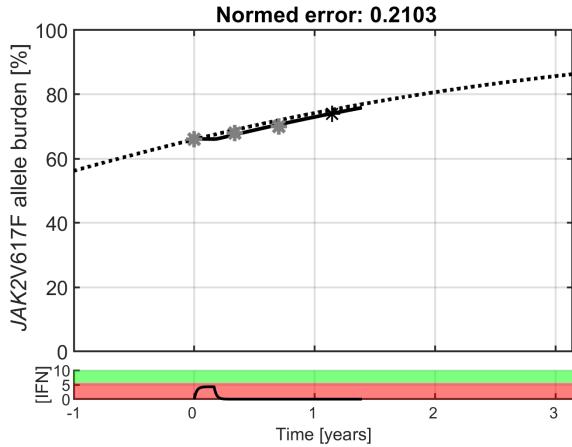


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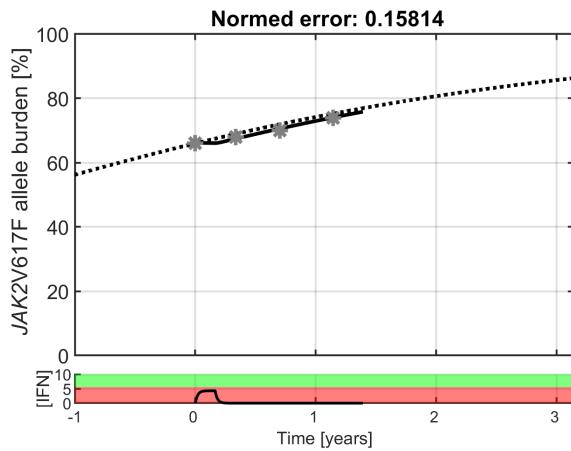


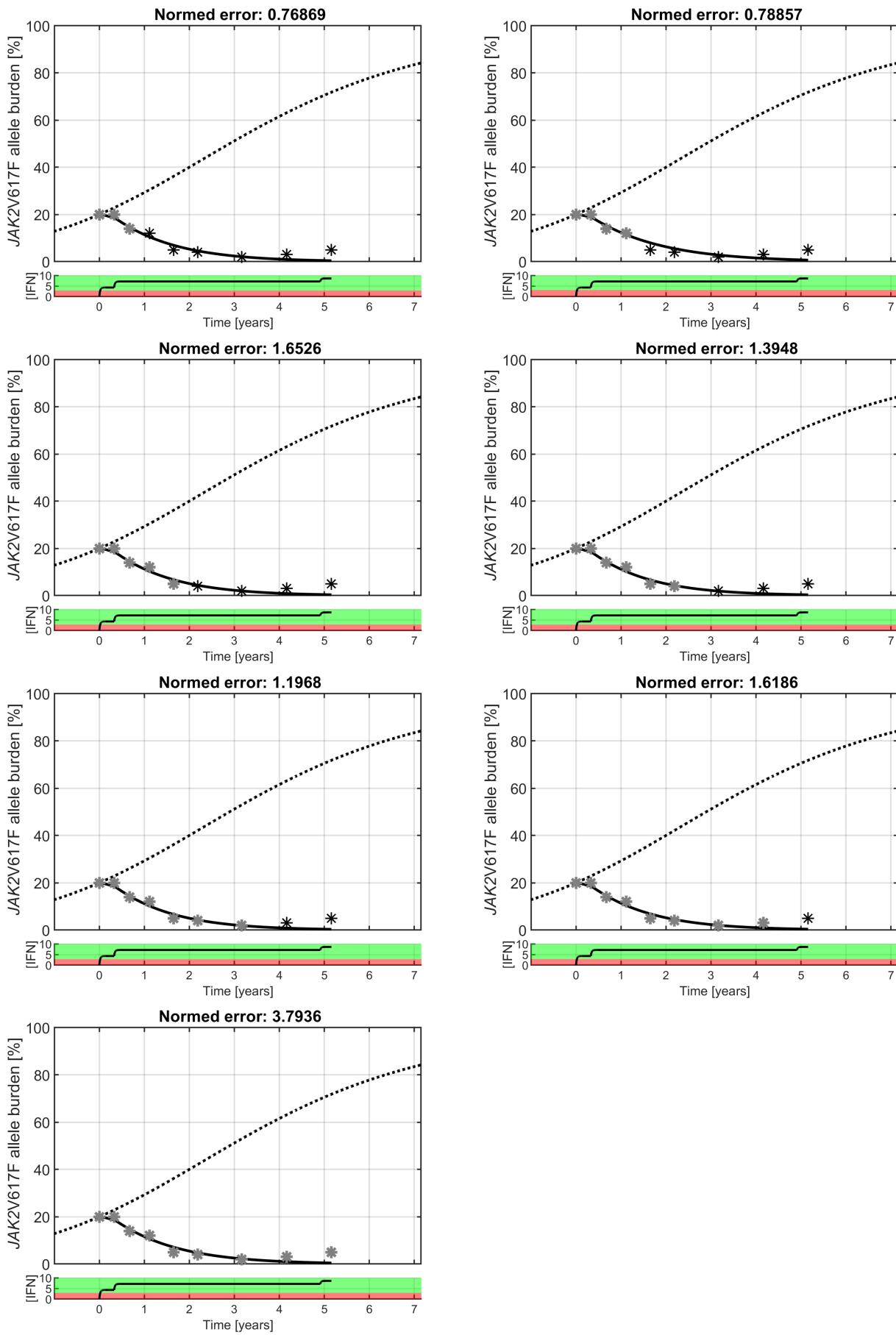


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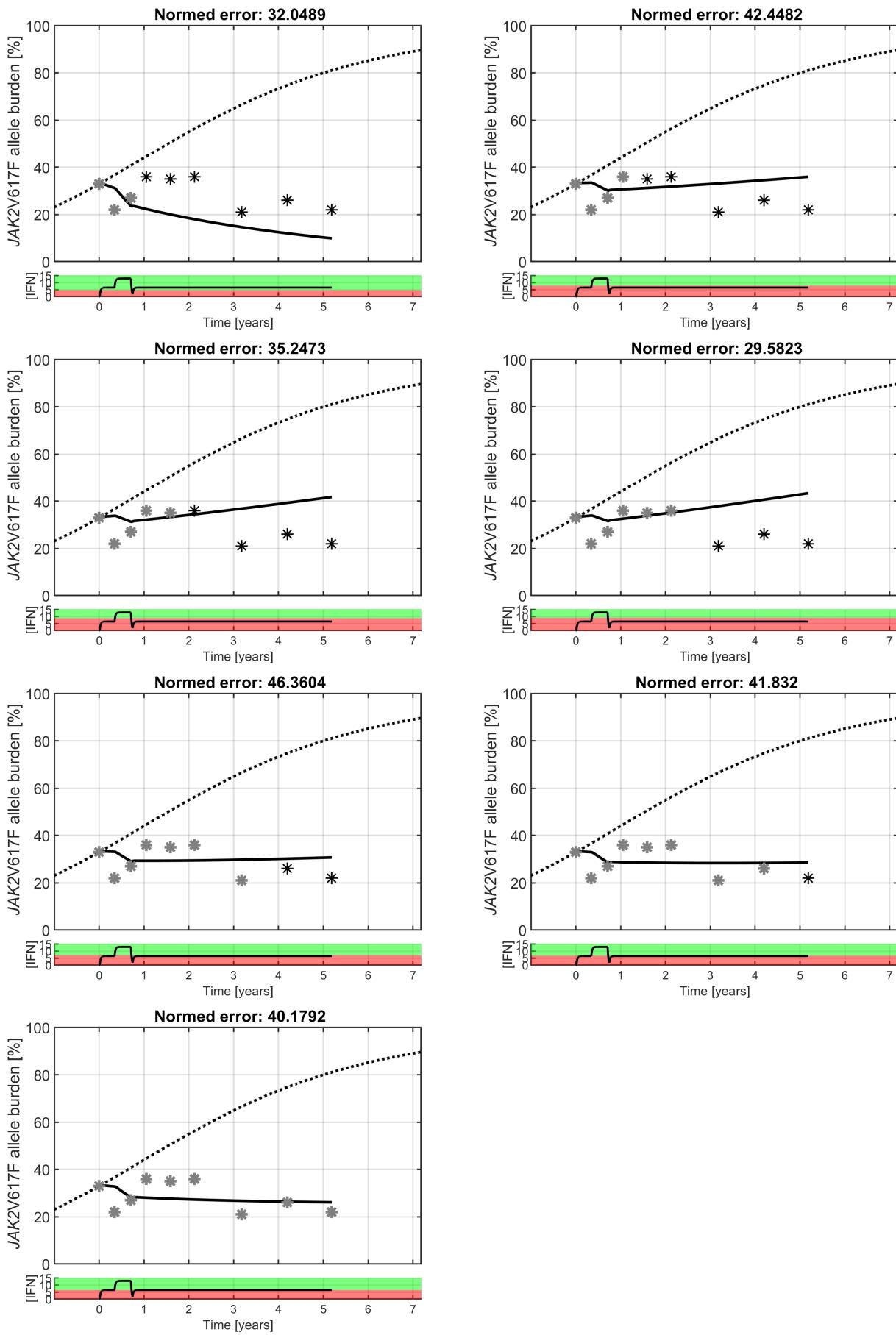


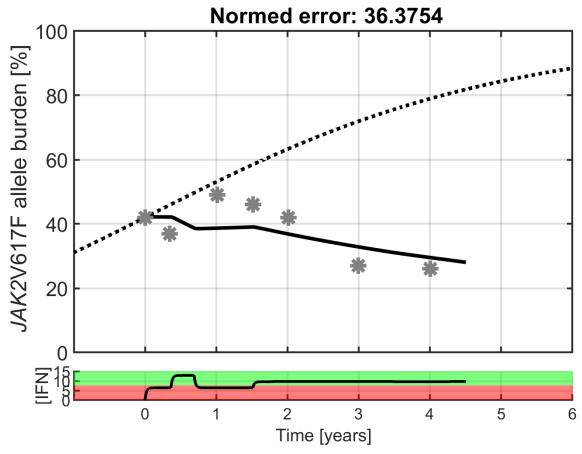
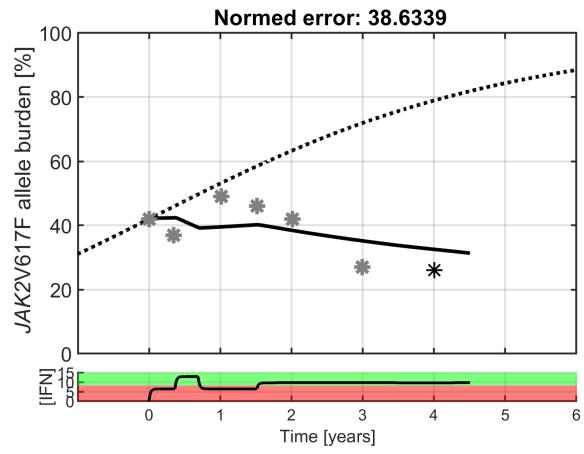
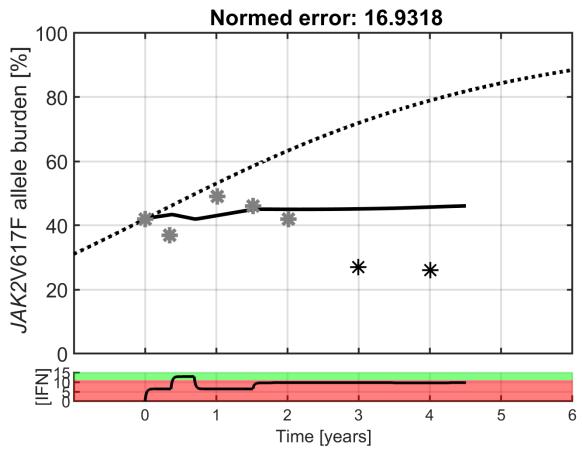
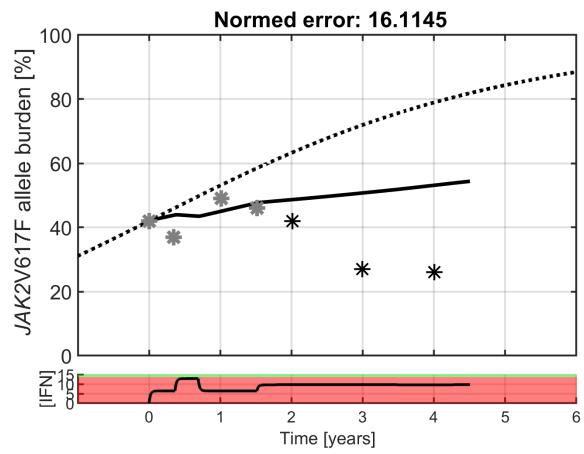
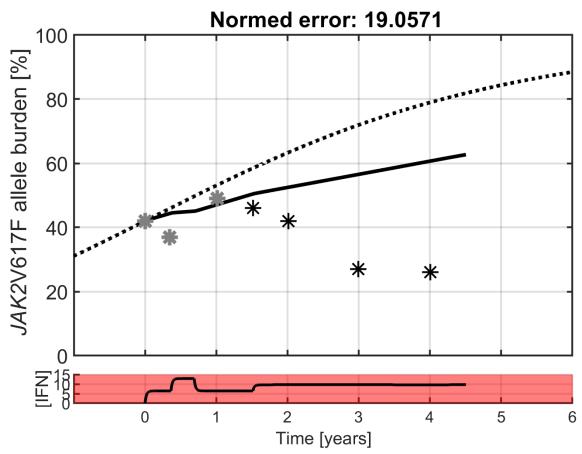
**Patient P028**



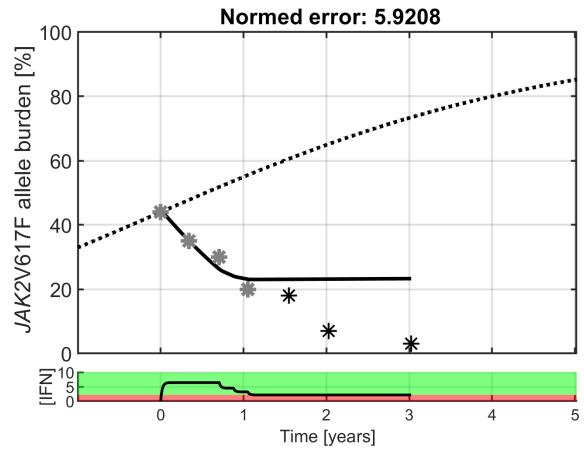
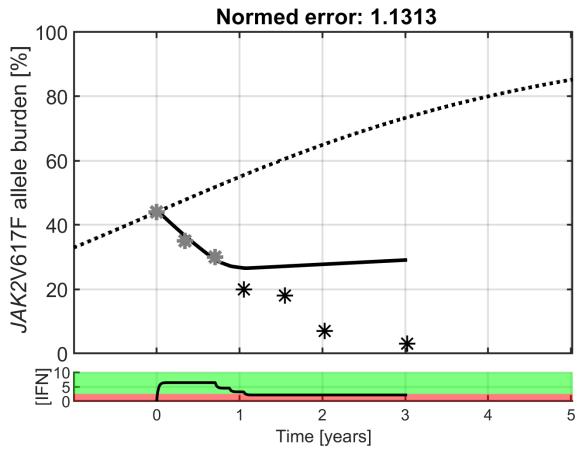


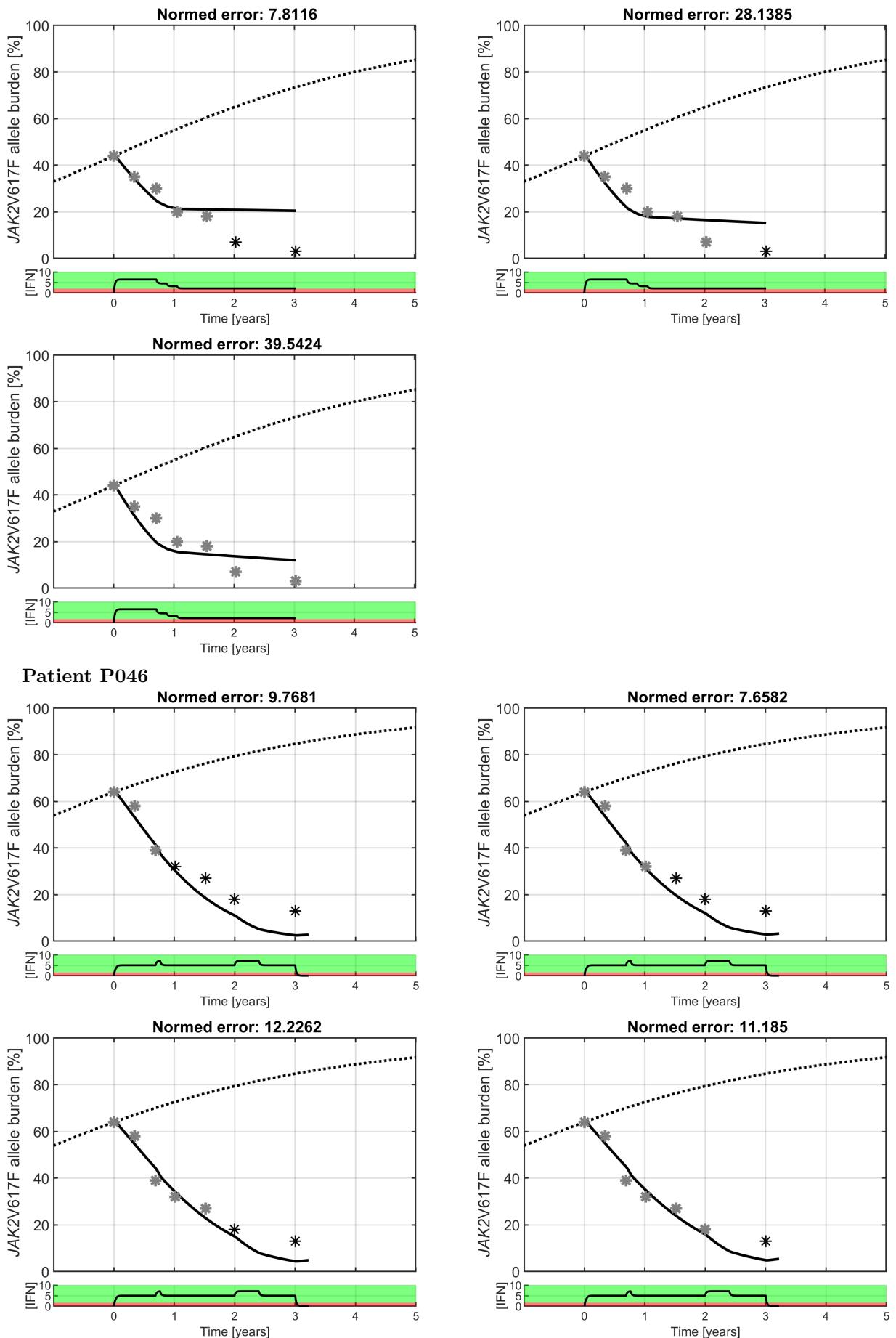
Patient P035

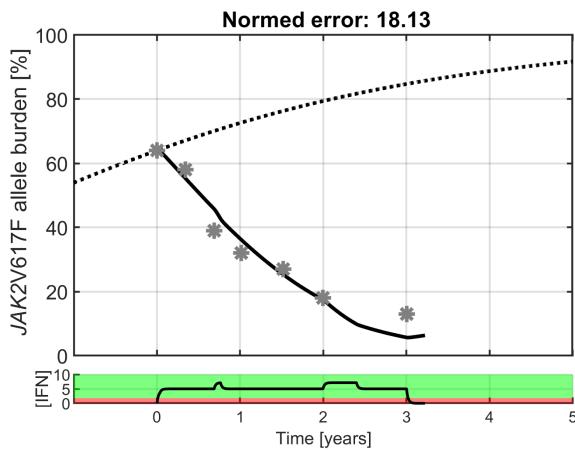




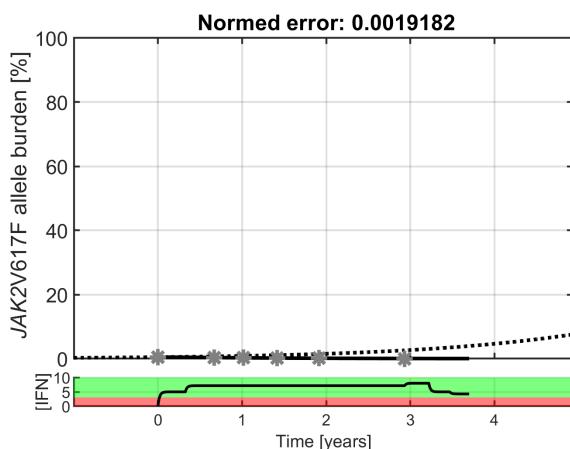
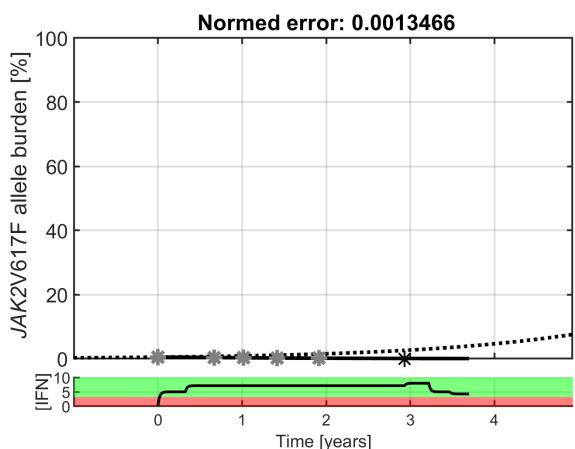
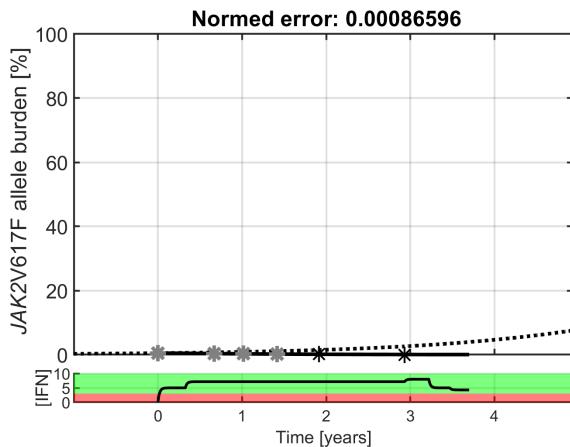
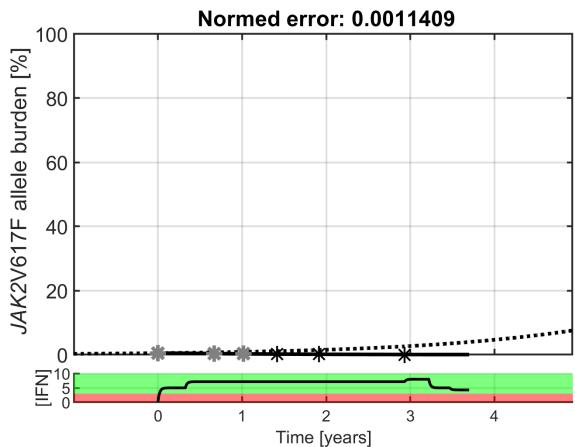
#### Patient P045



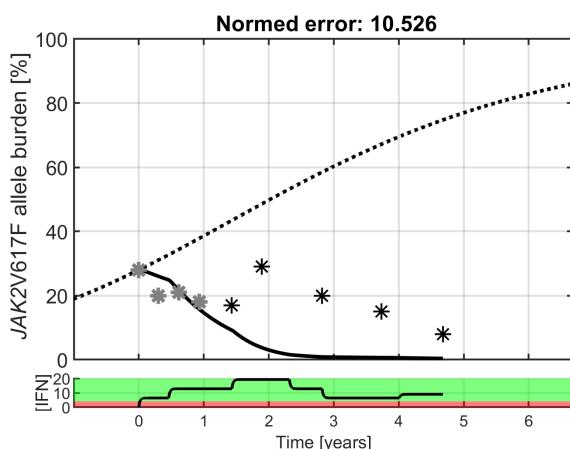
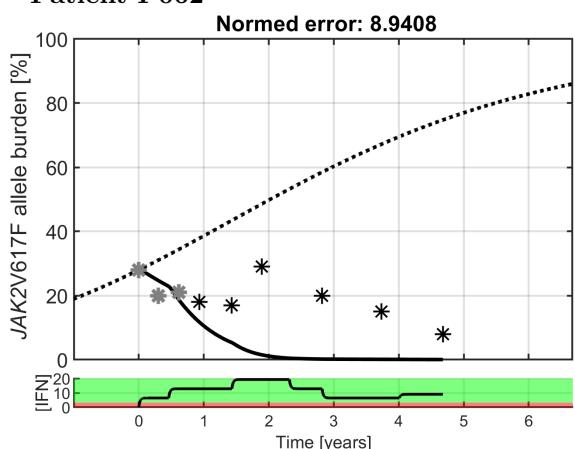


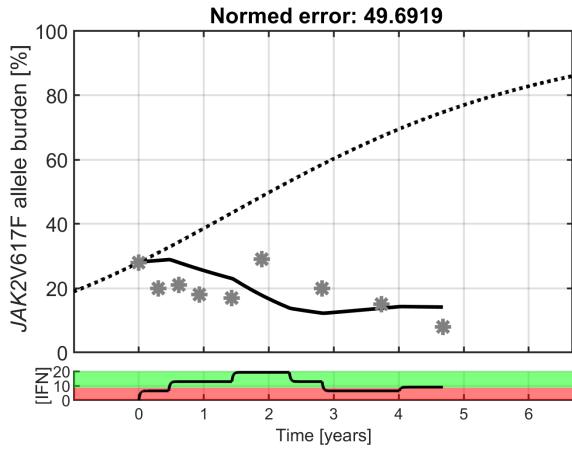
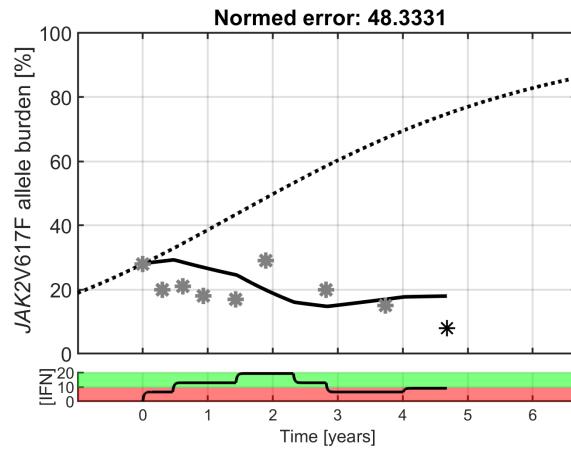
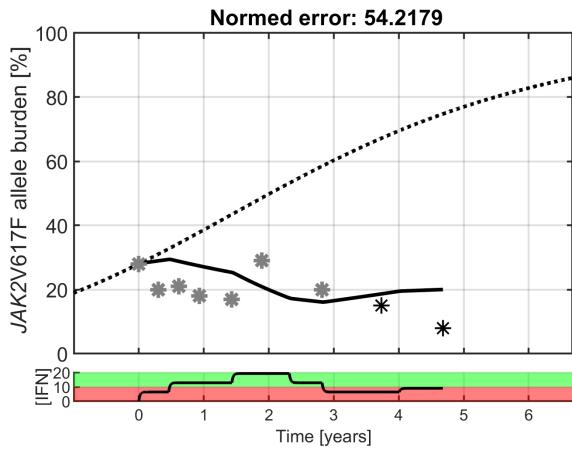
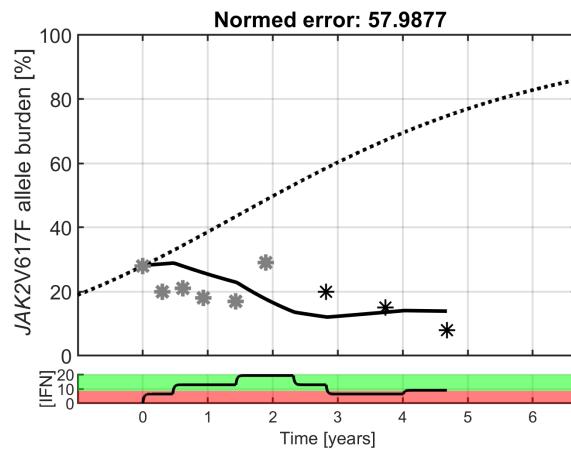
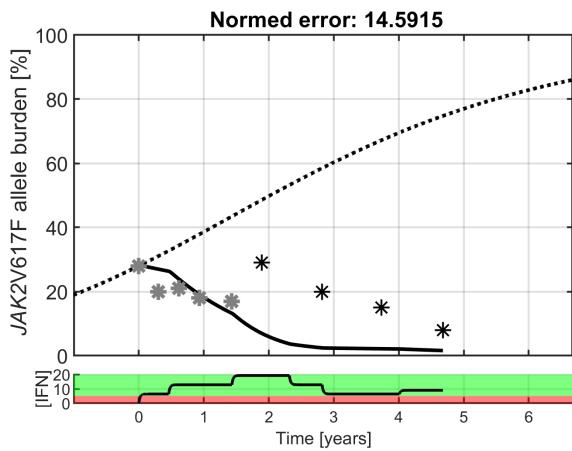


Patient P046

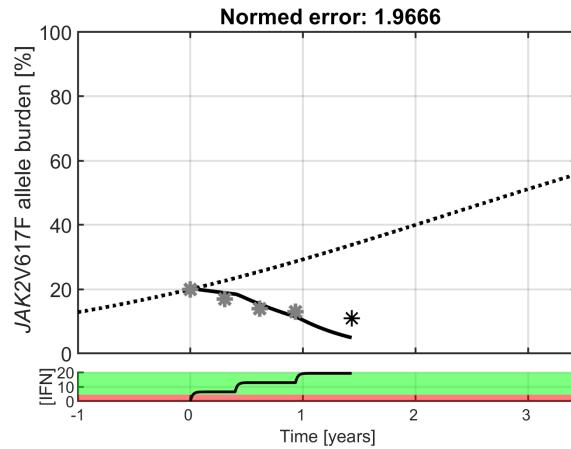
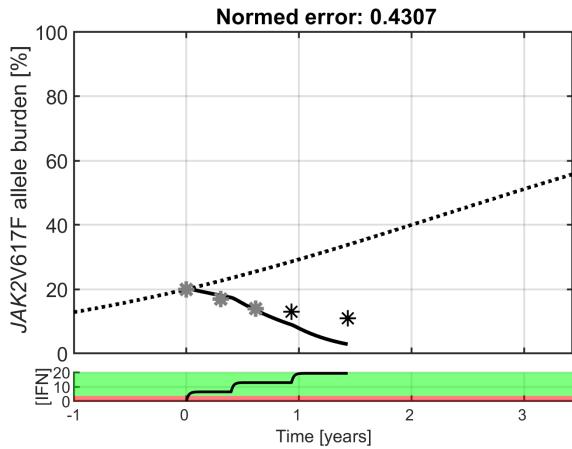


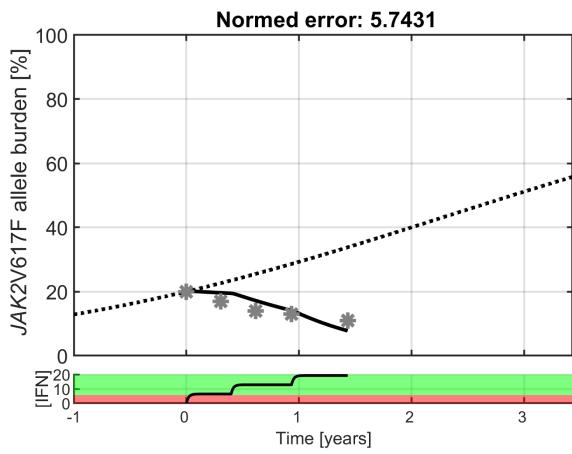
Patient P062



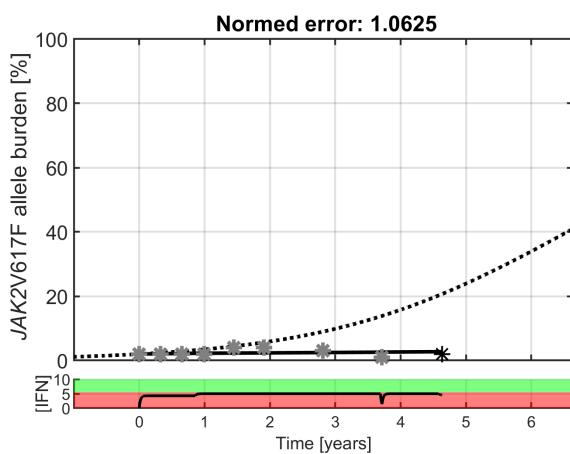
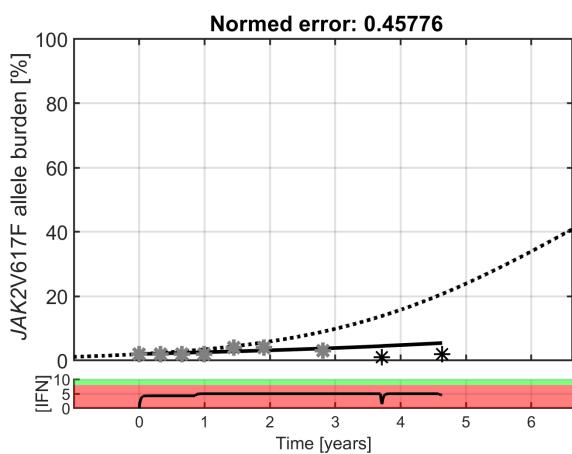
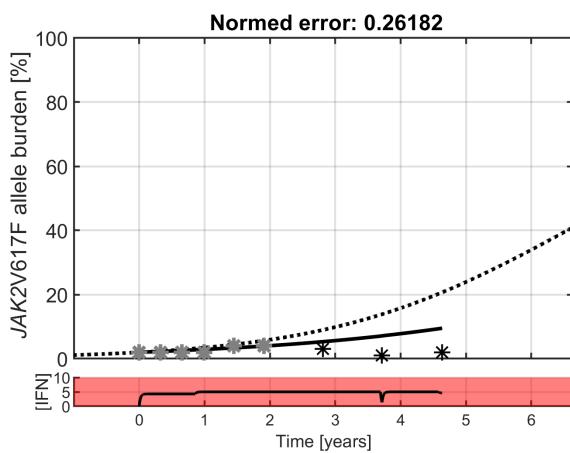
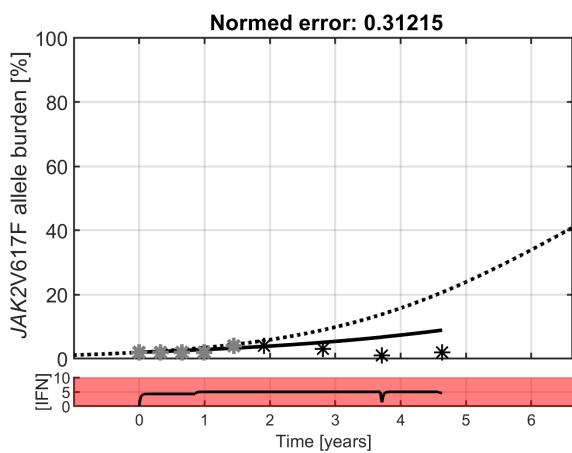
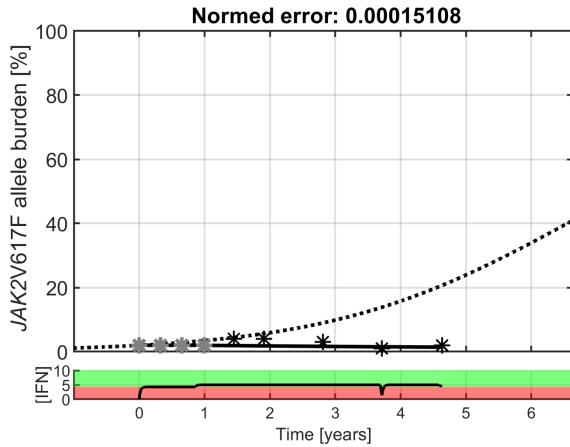
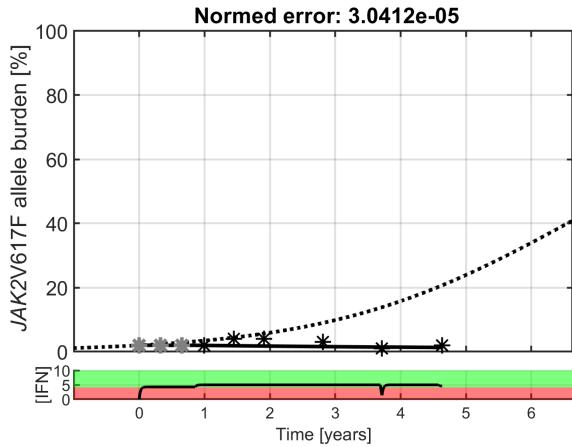


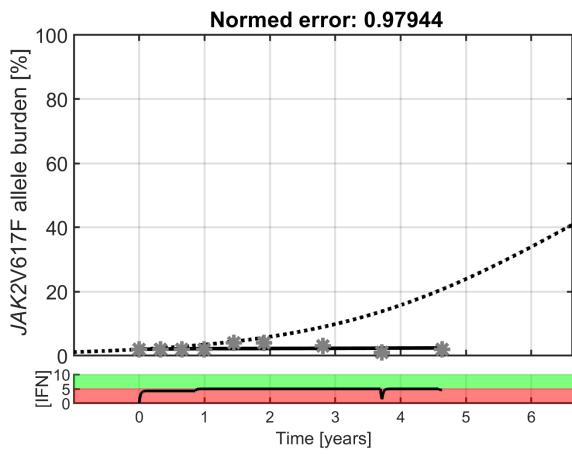
### Patient P067



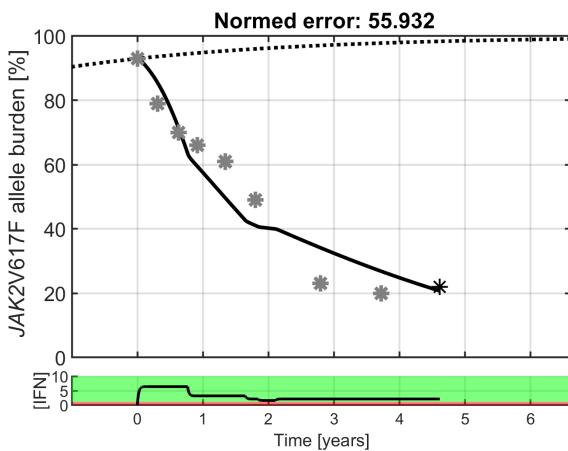
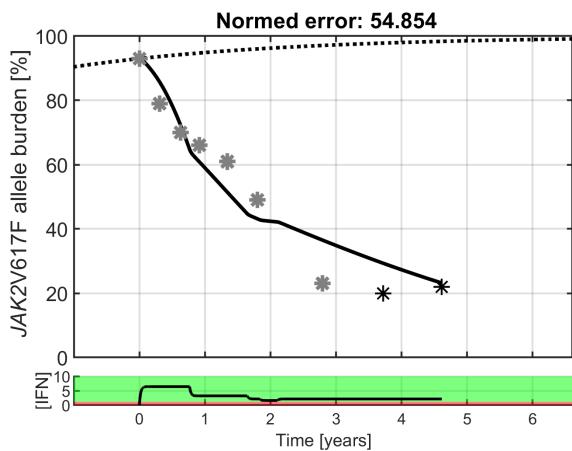
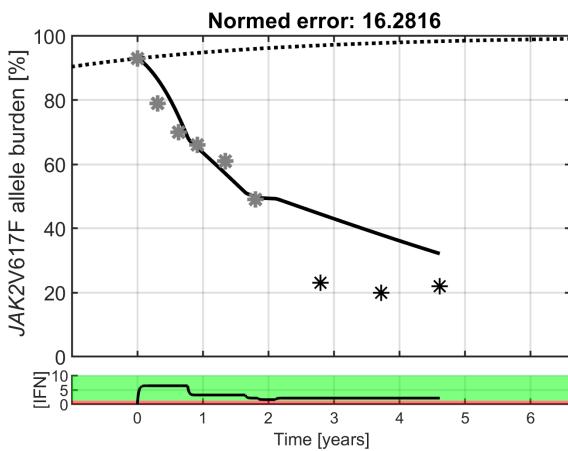
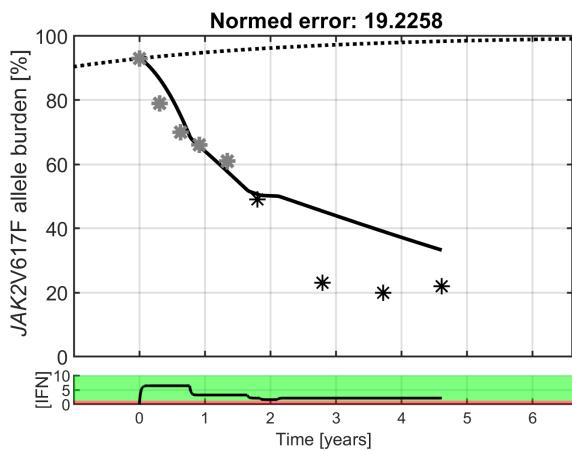
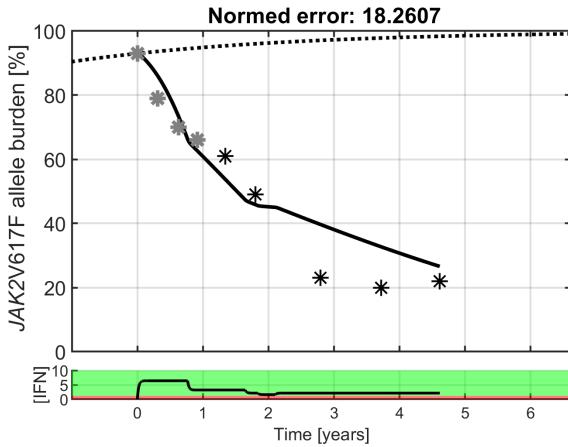
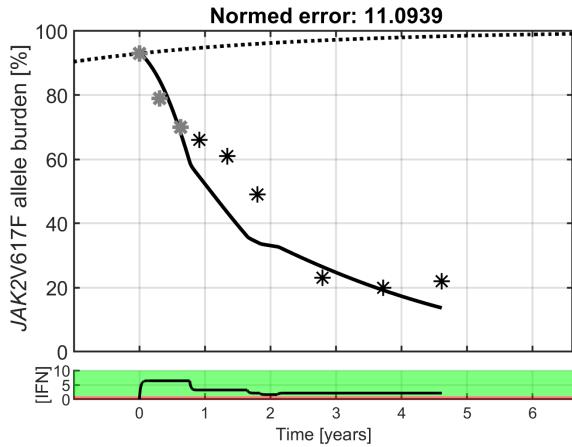


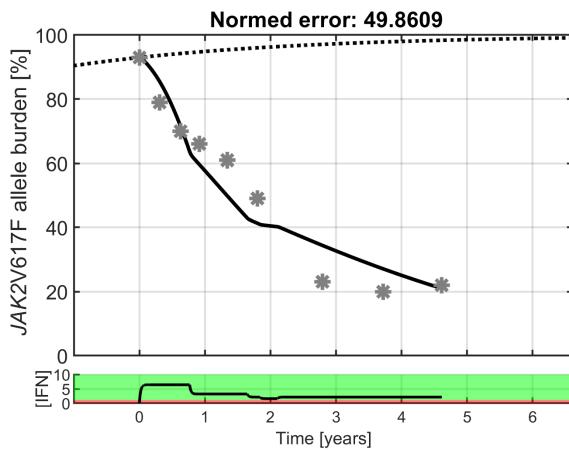
Patient P070



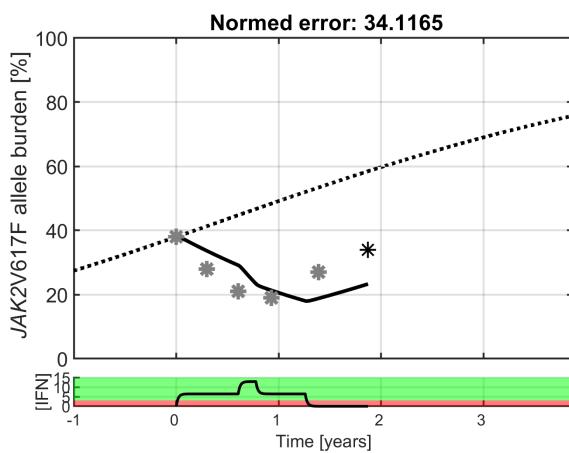
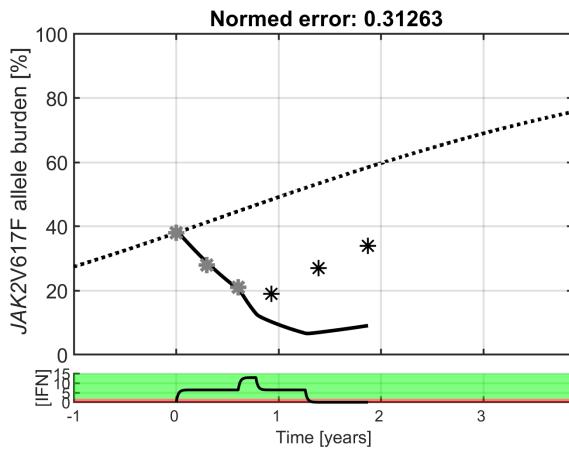


Patient P075

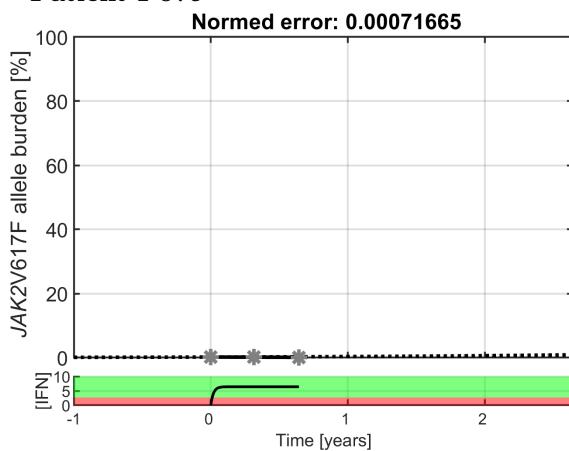




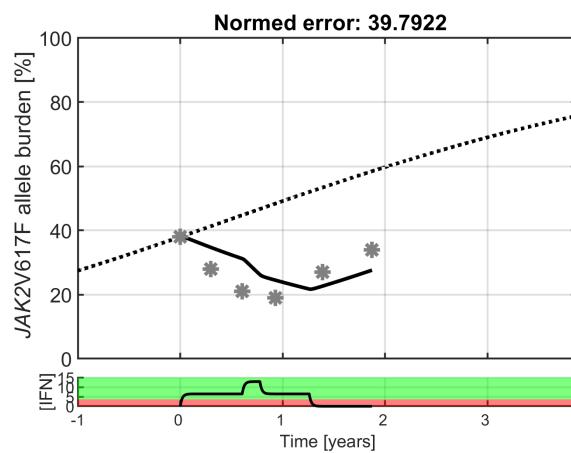
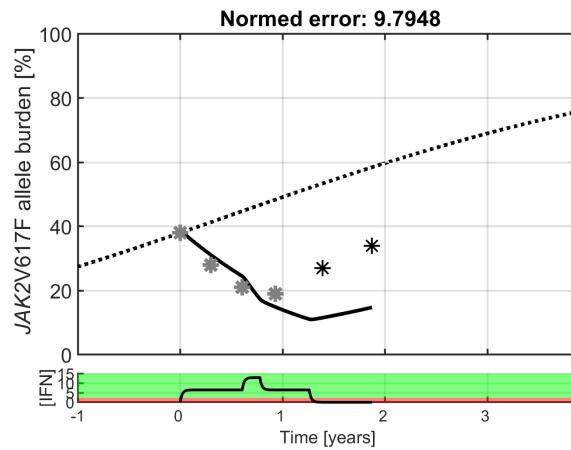
Patient P078

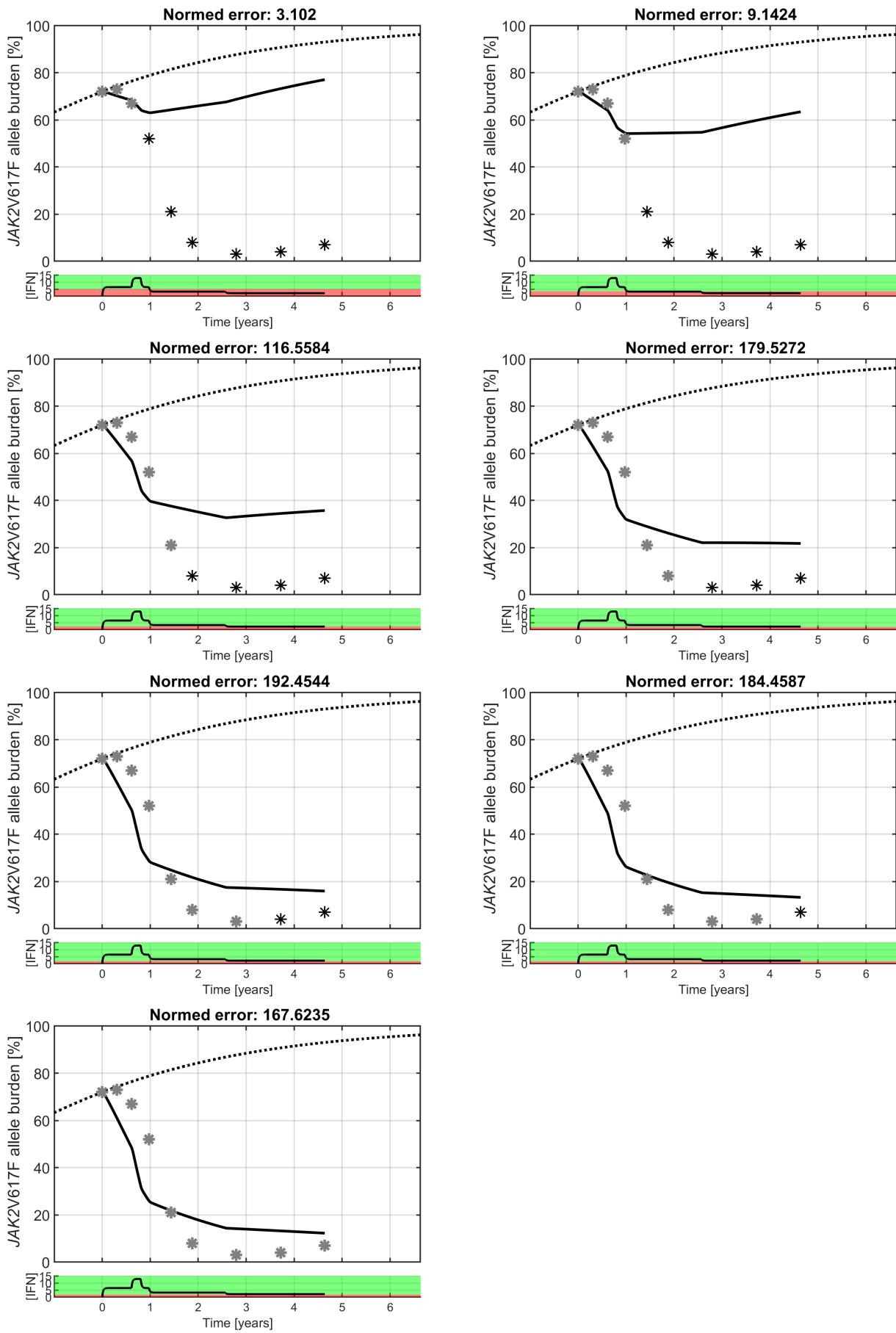


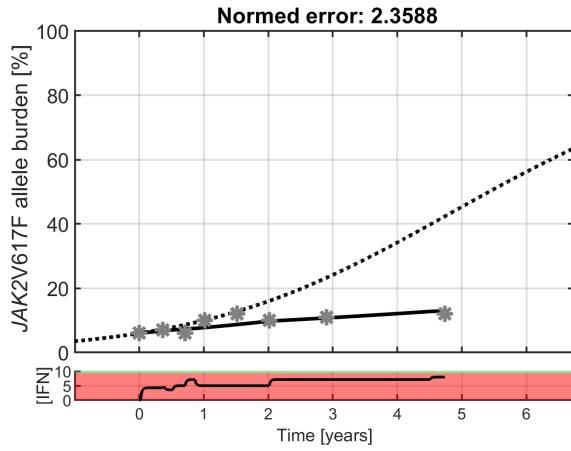
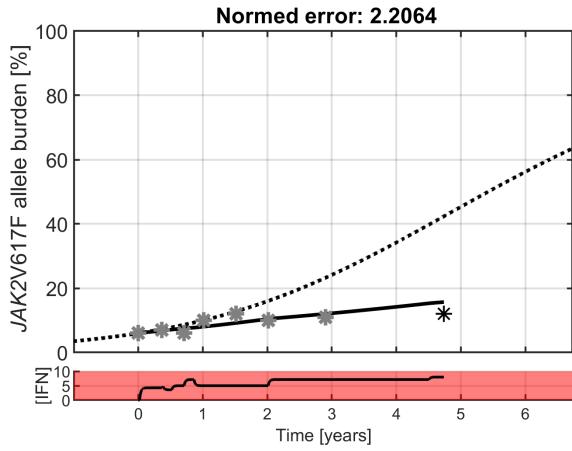
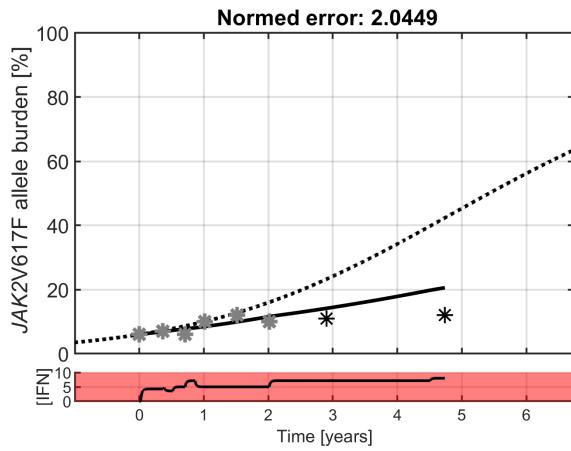
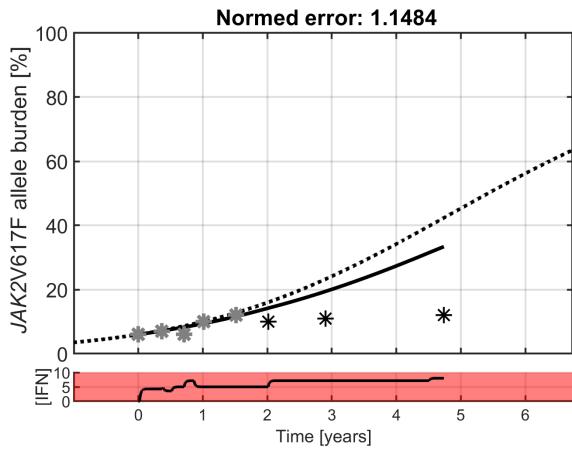
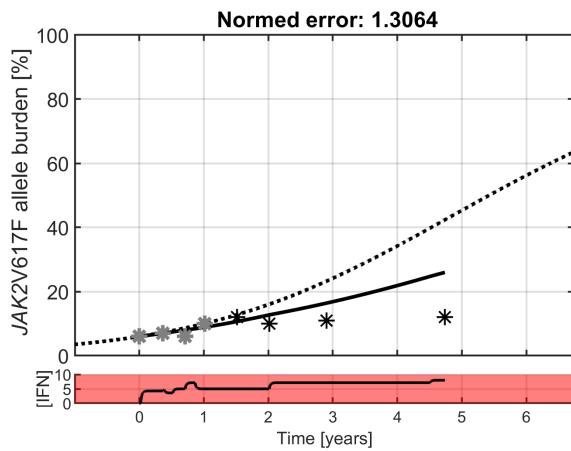
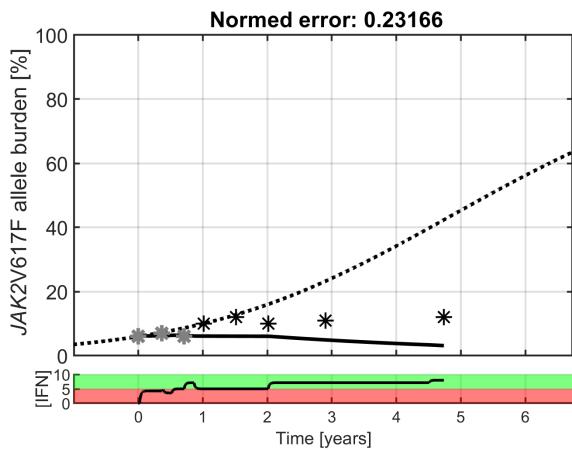
Patient P079



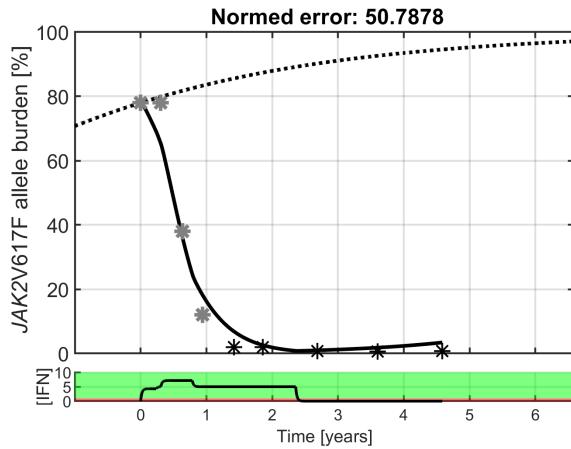
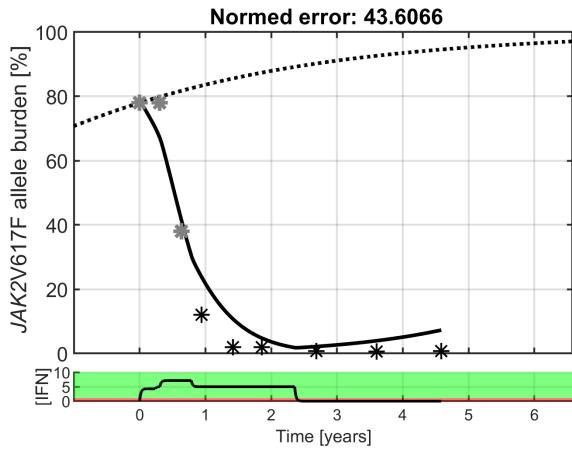
Patient P082

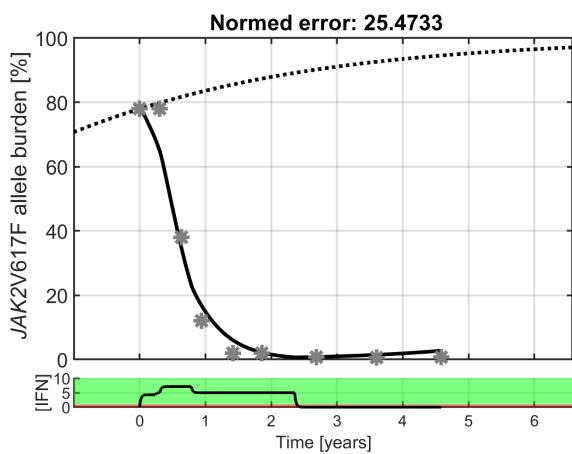
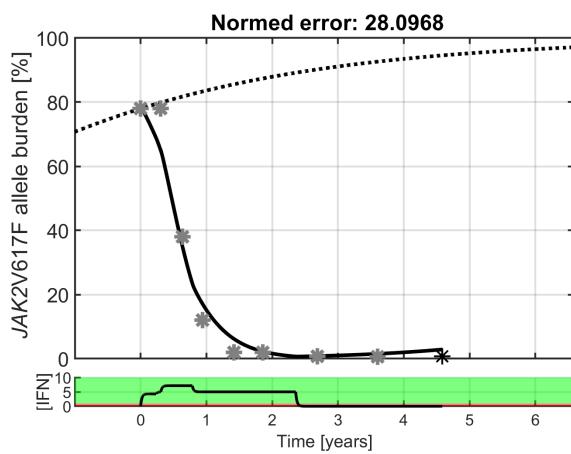
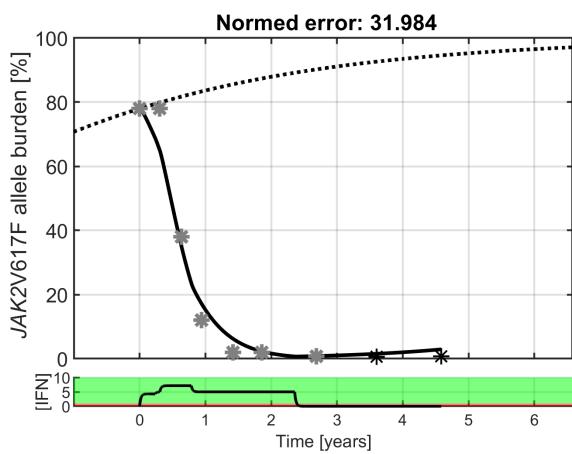
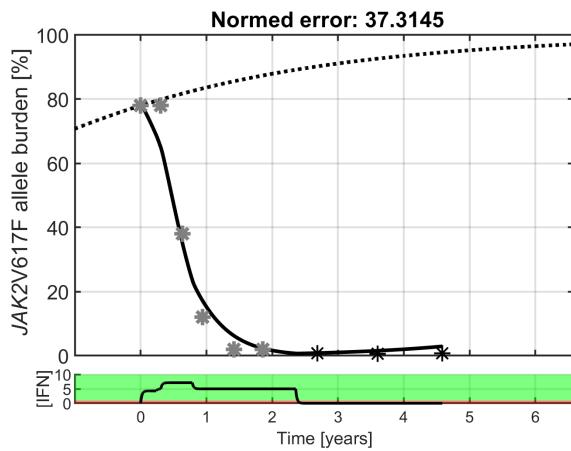
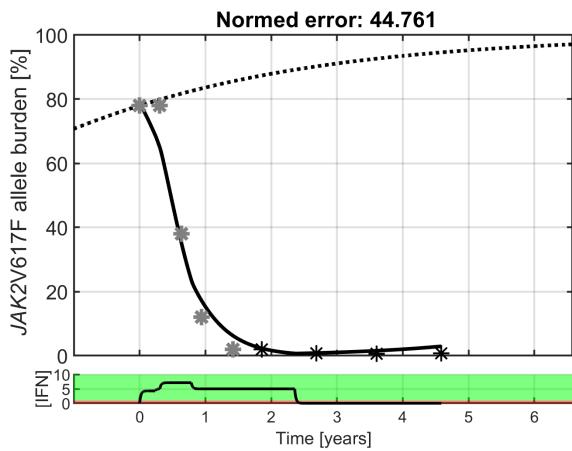




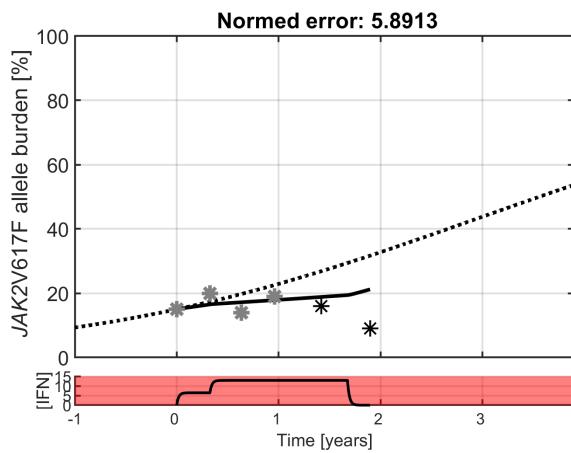
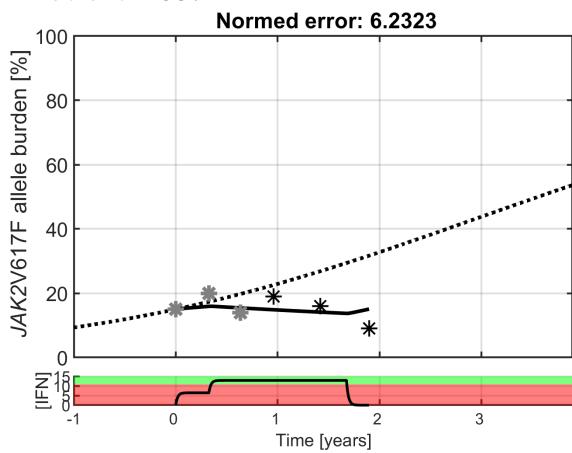


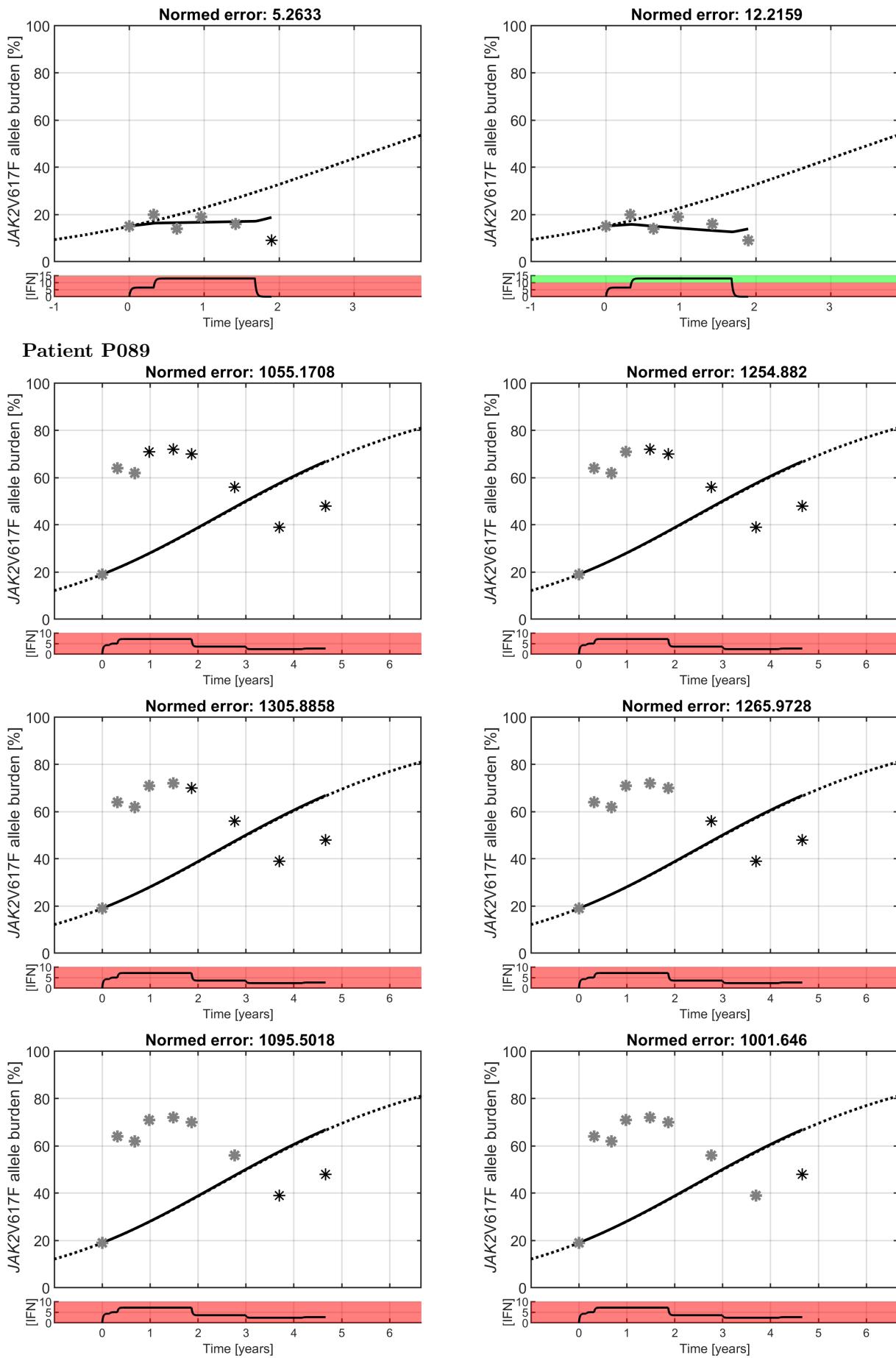
### Patient P086

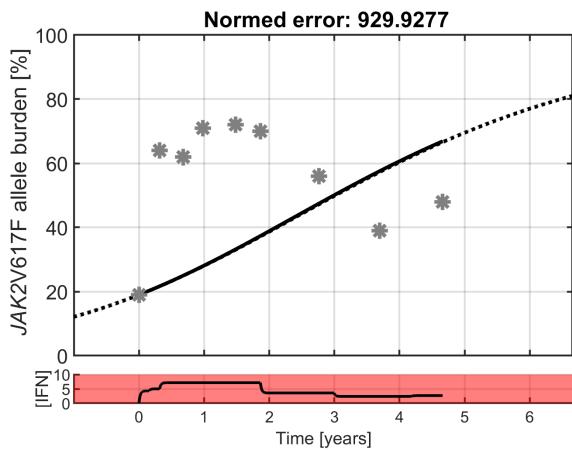




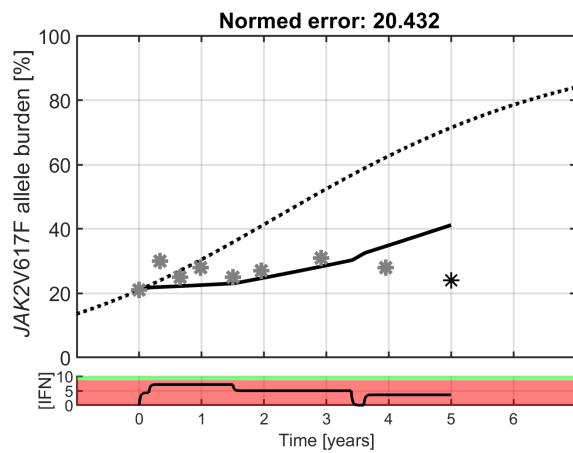
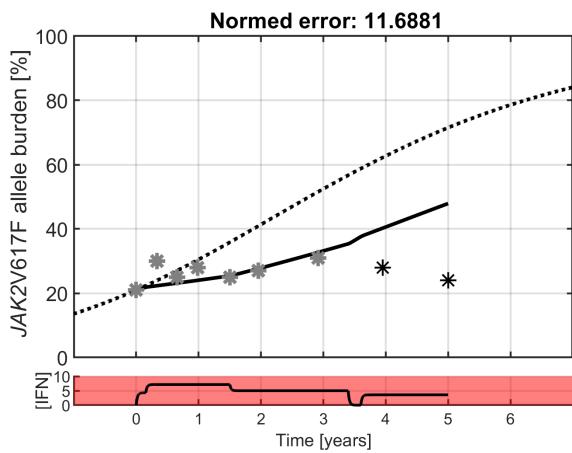
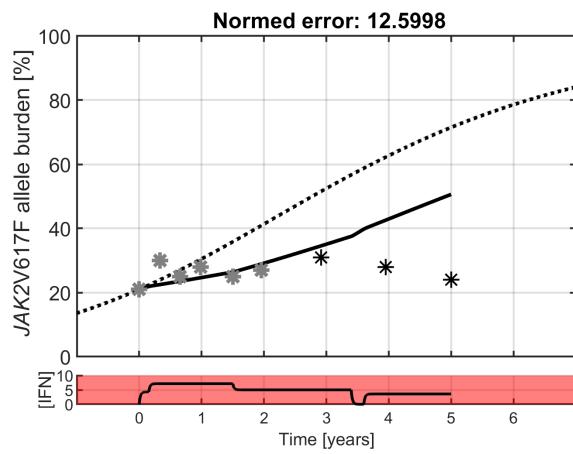
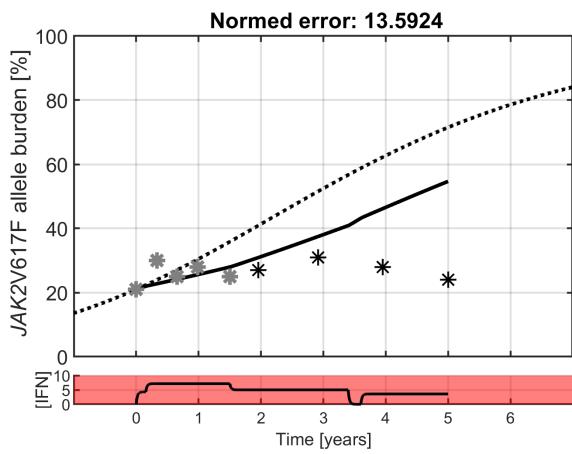
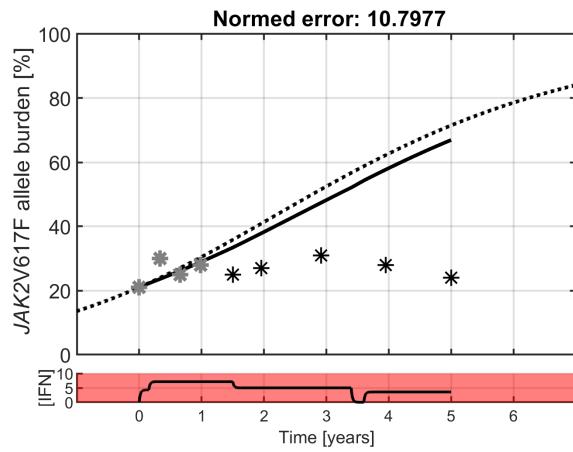
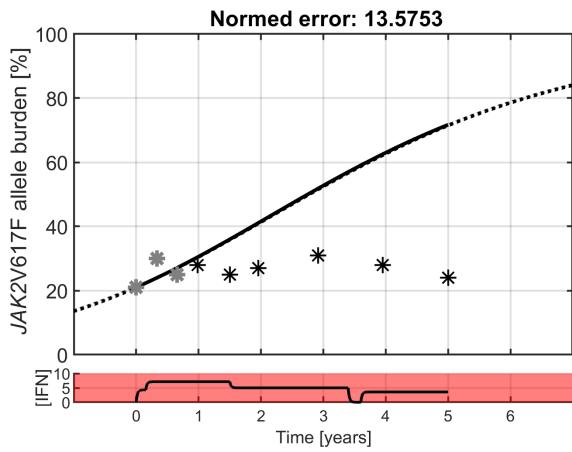
### Patient P087

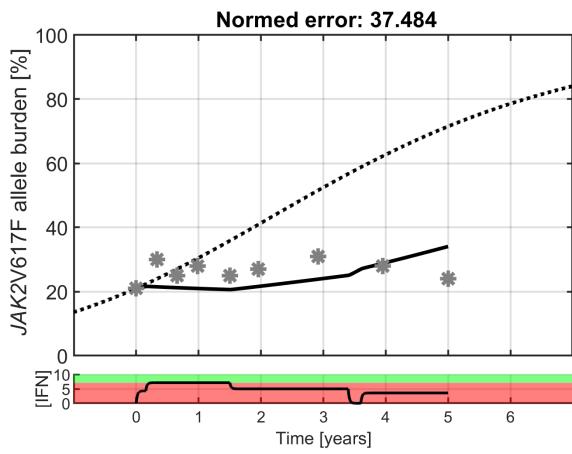




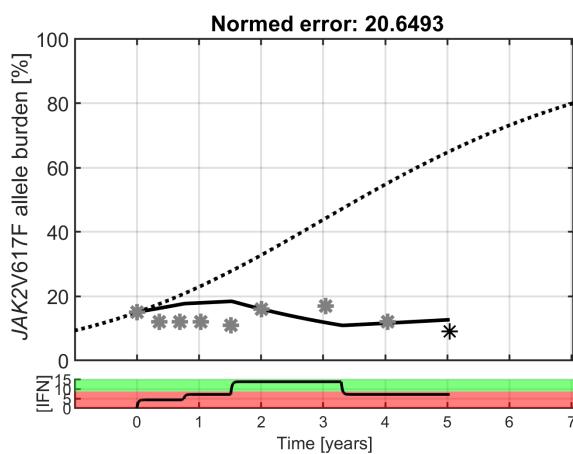
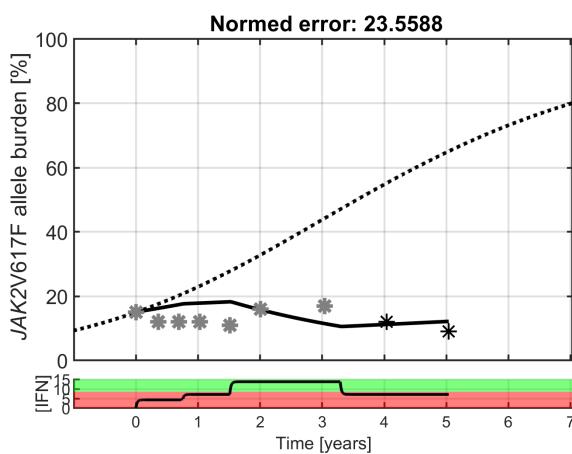
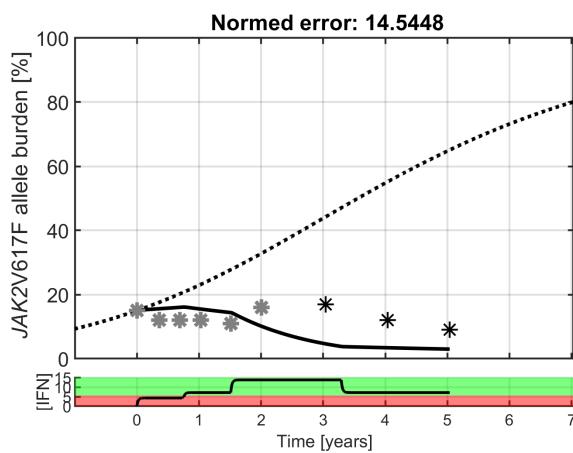
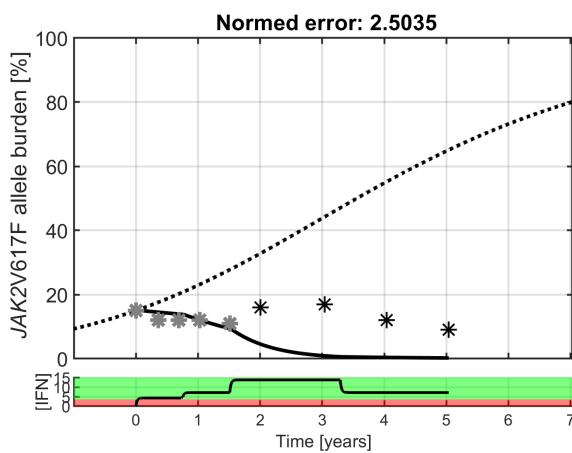
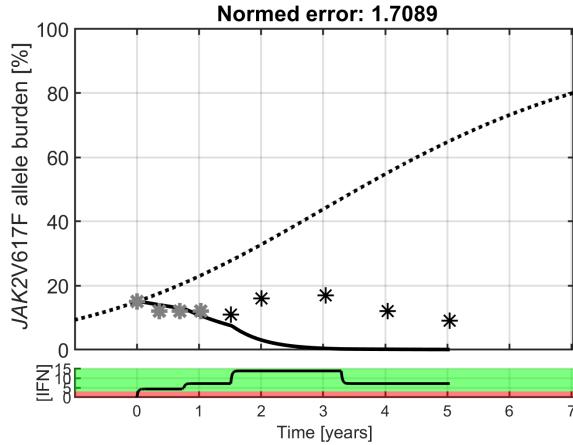
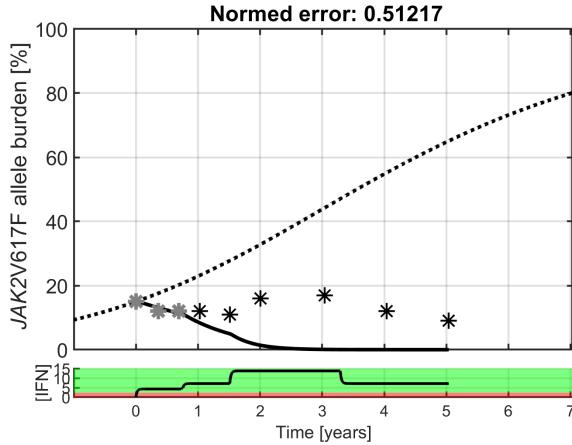


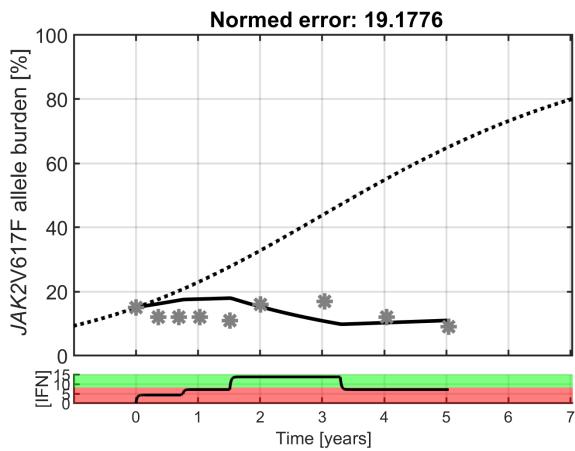
Patient P105



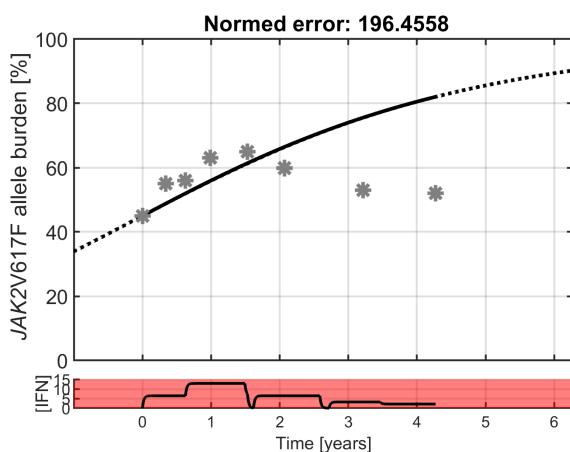
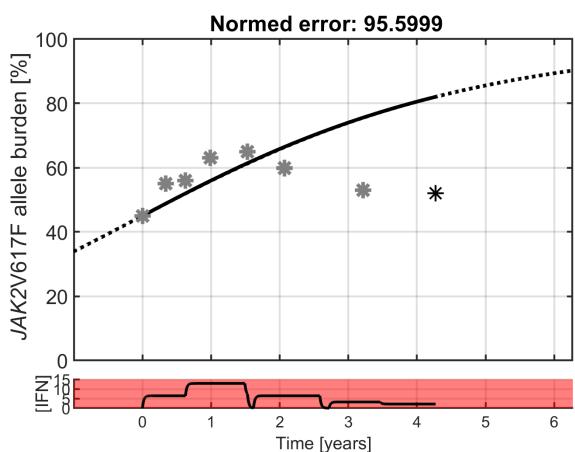
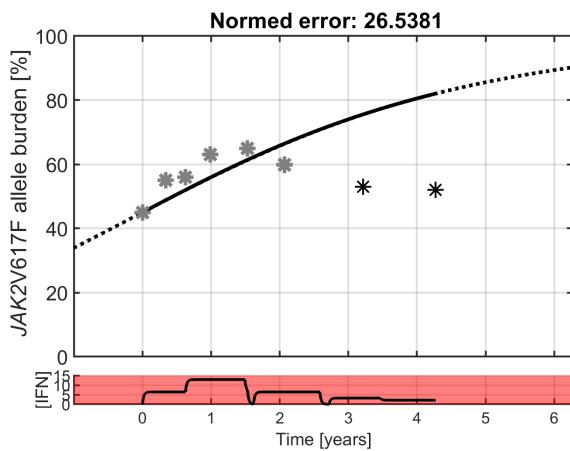
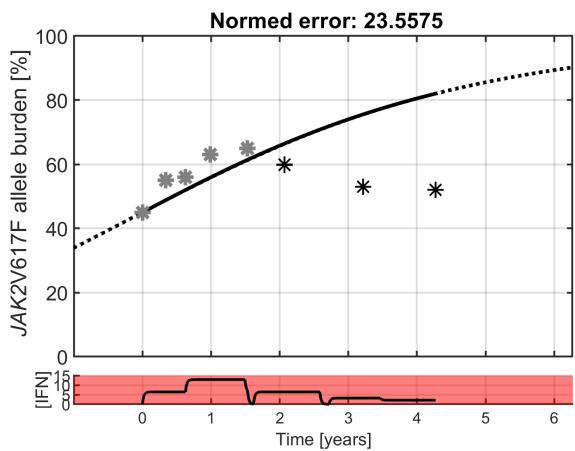
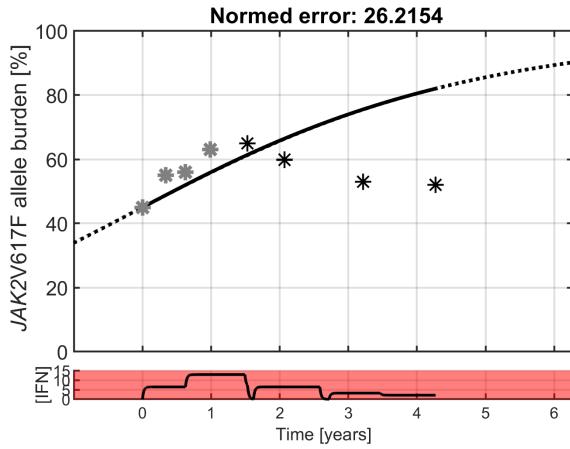
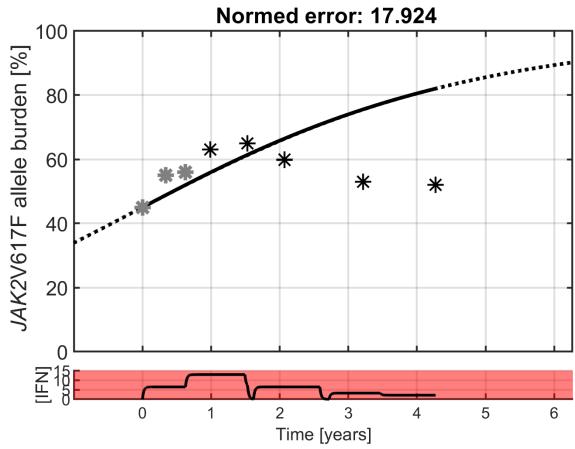


Patient P106

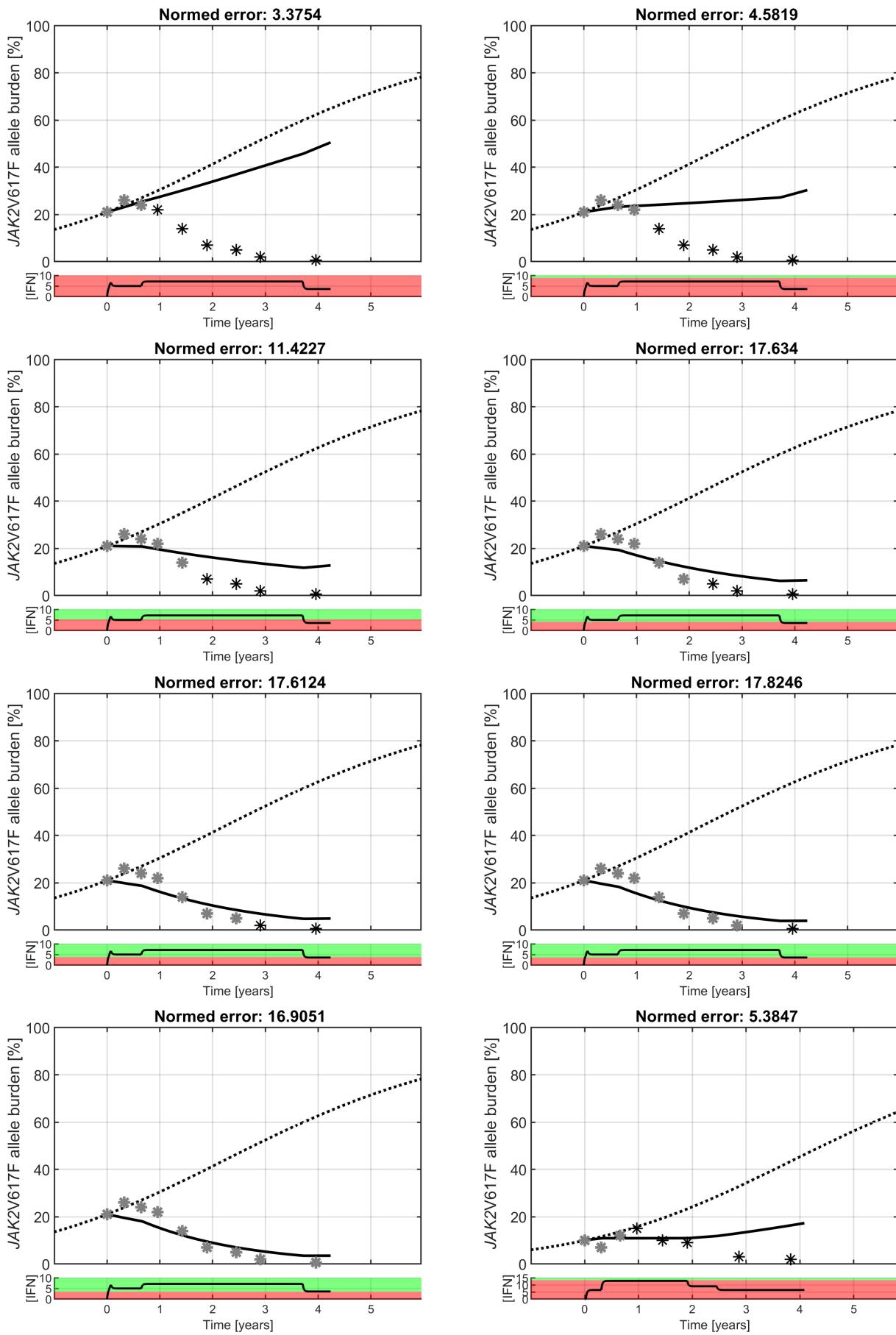


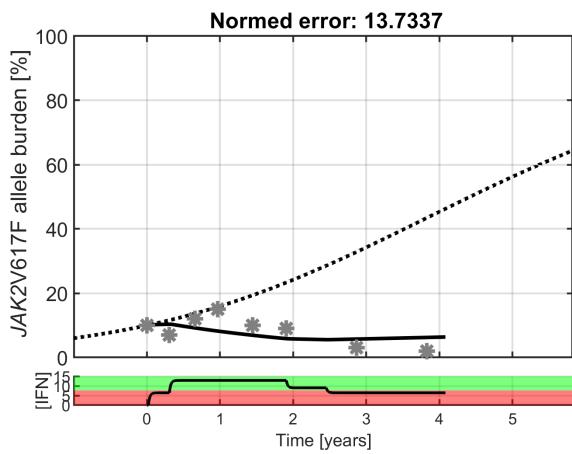
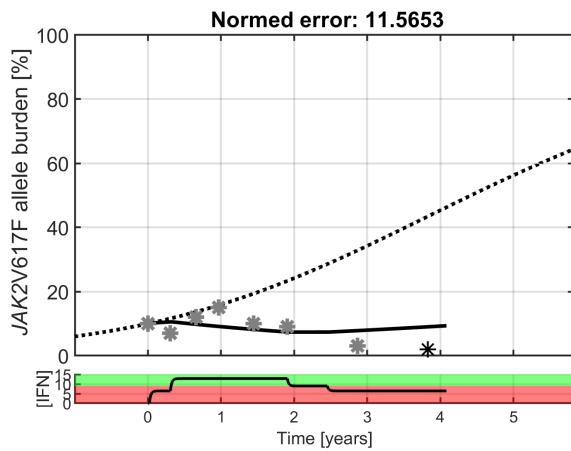
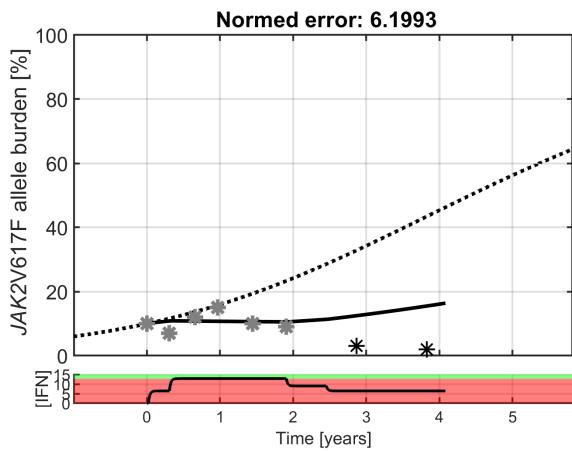
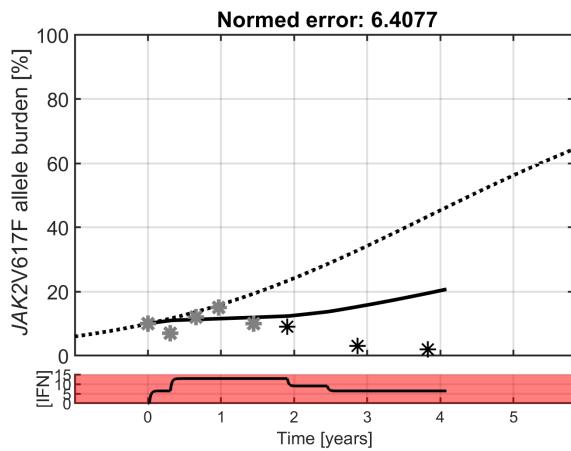
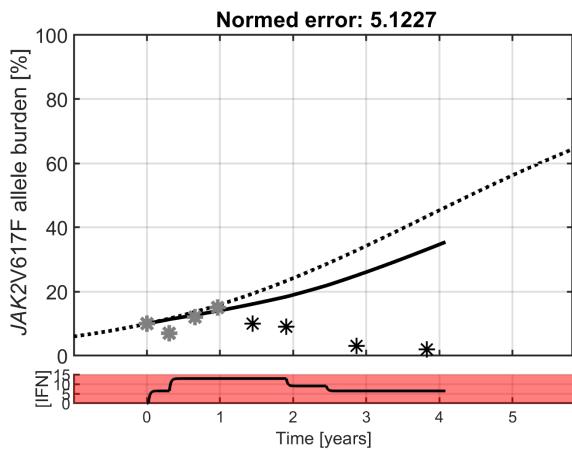


Patient P111

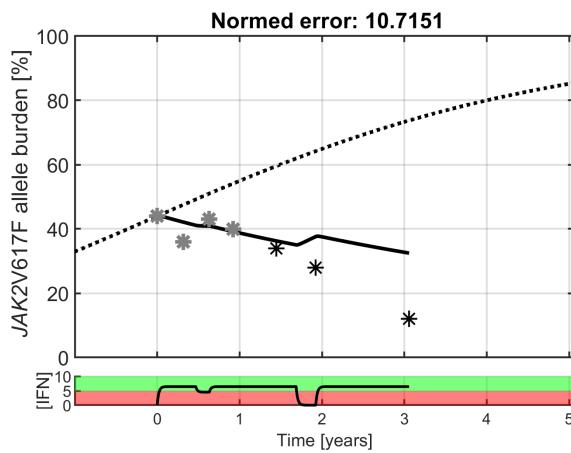
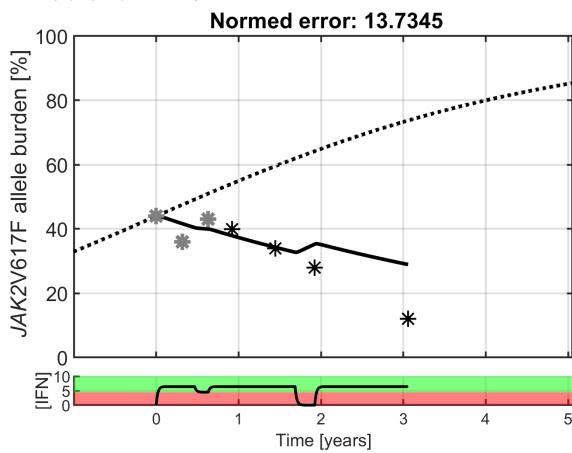


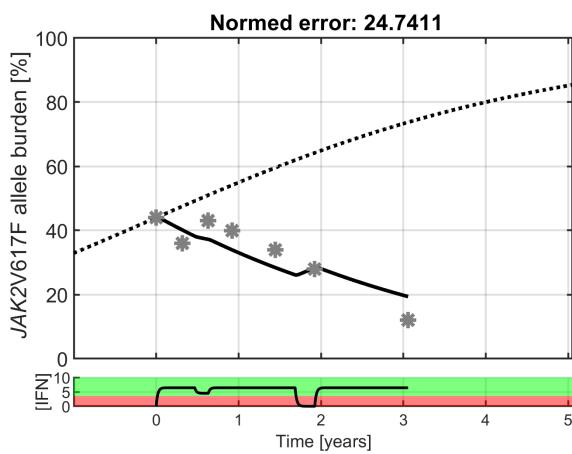
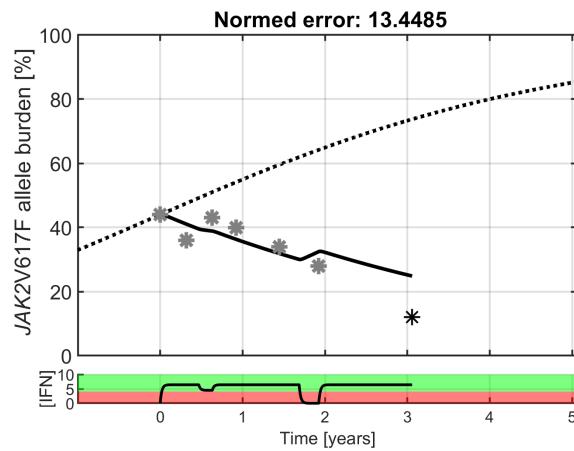
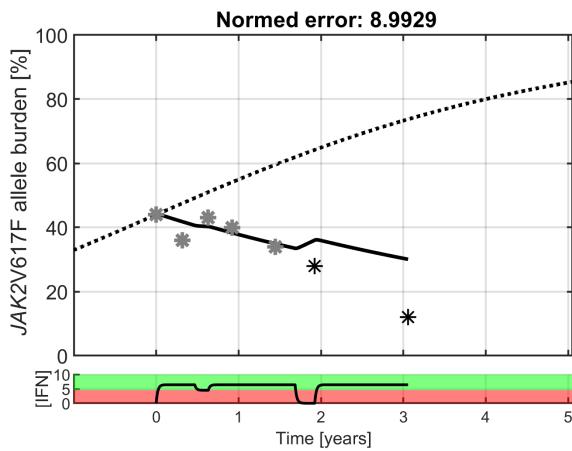
Patient P113



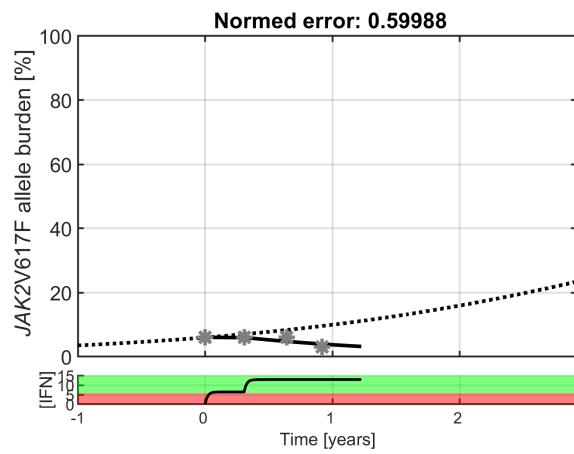
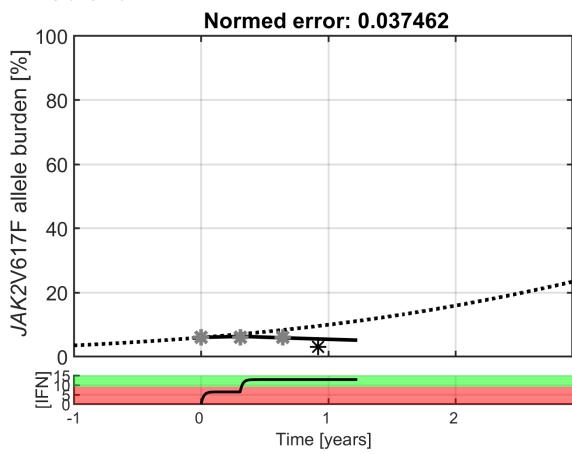


### Patient P117

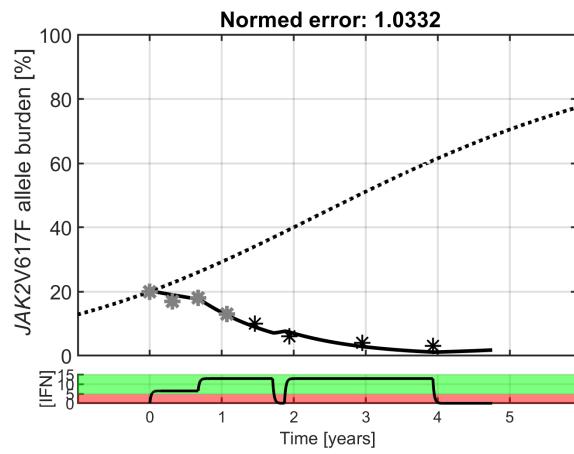
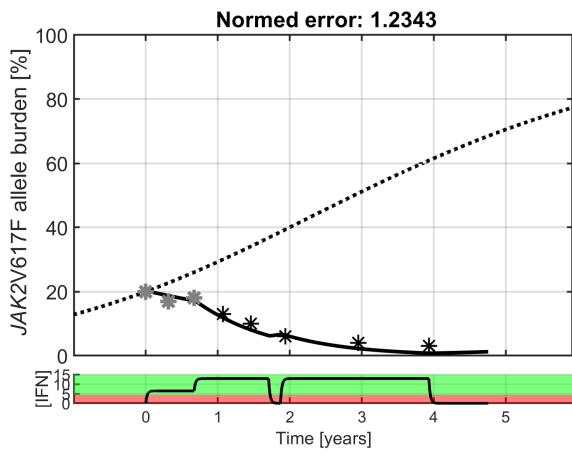


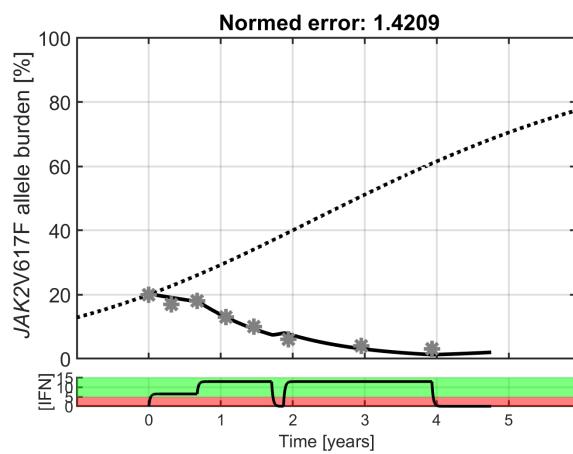
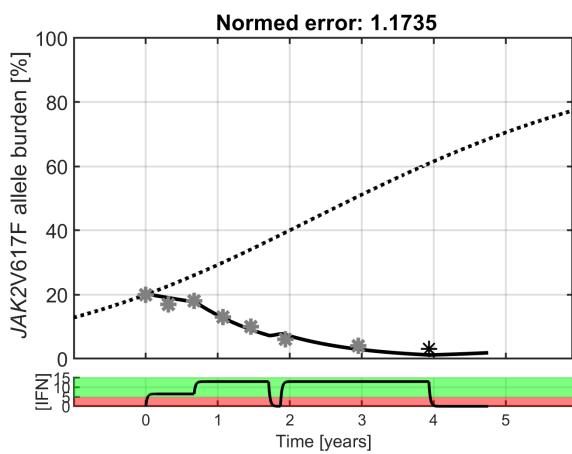
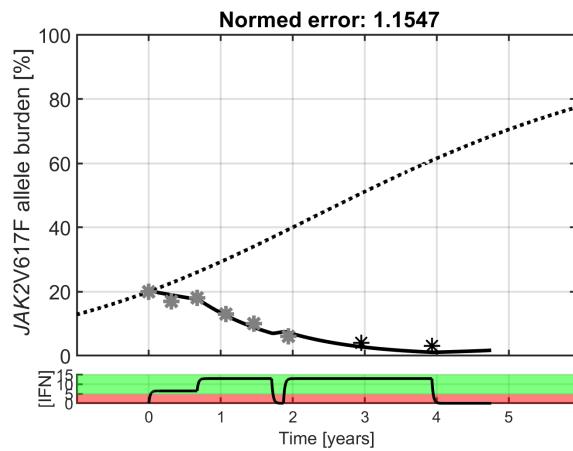
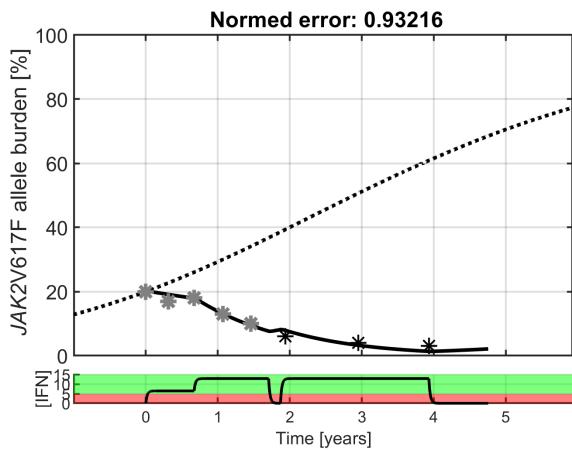


Patient P122

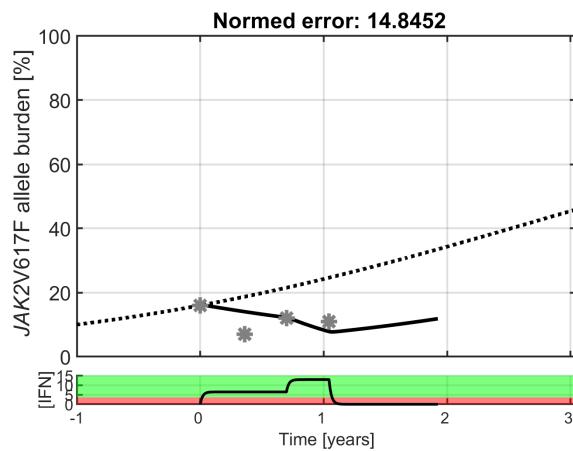
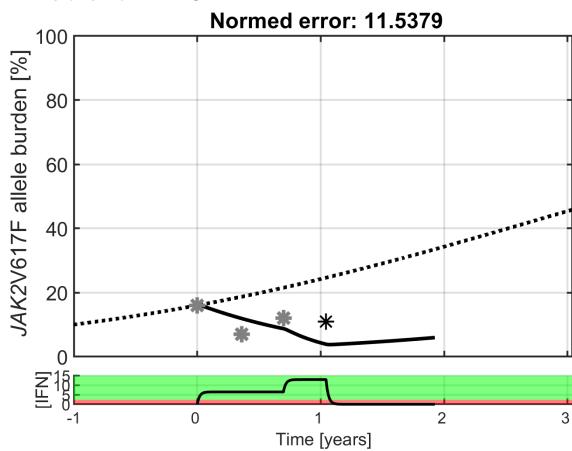


Patient P124

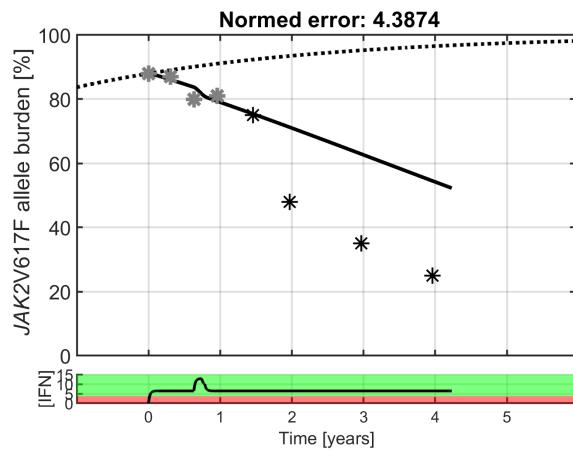
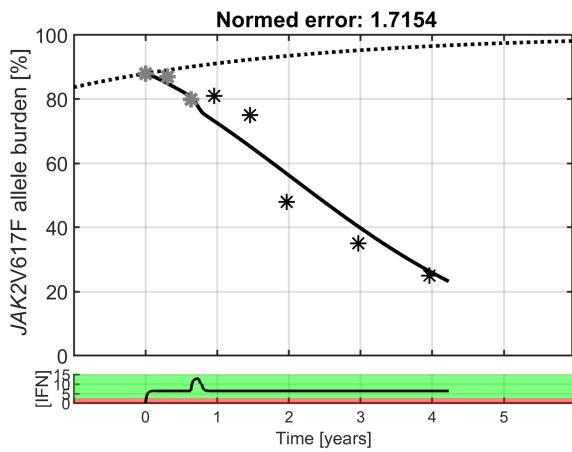


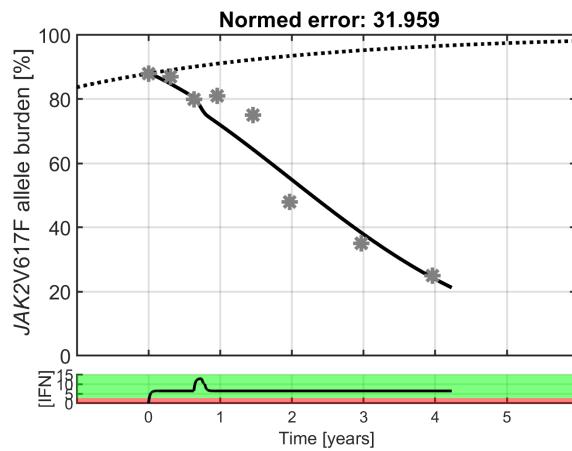
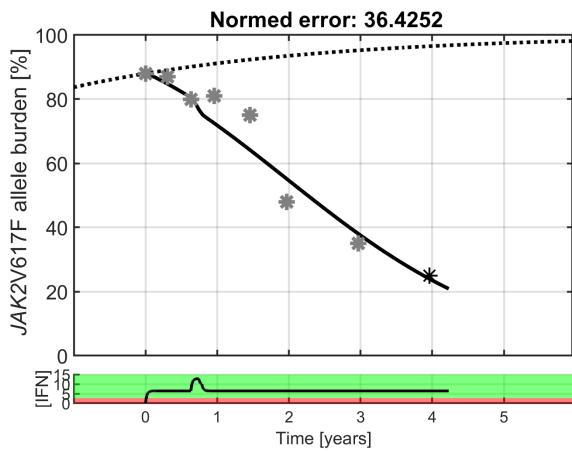
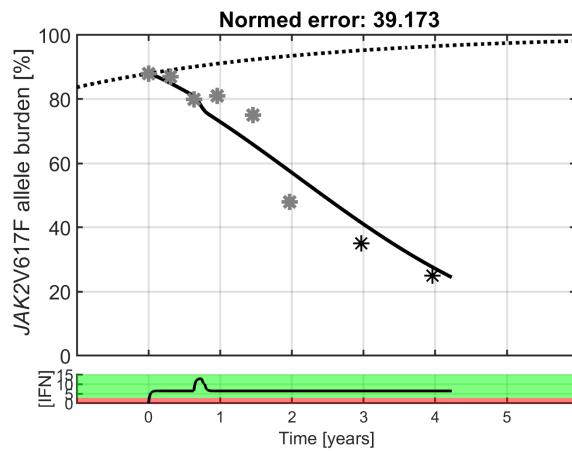
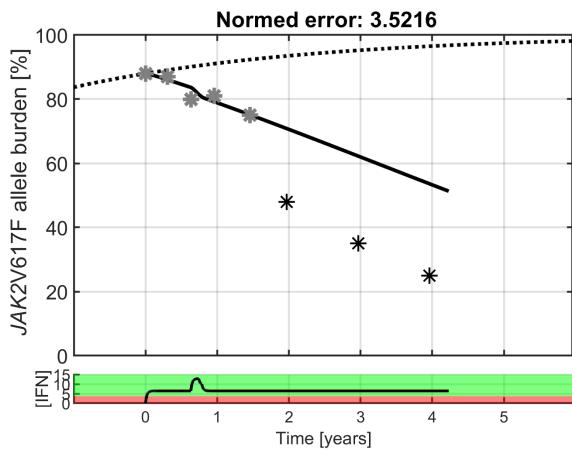


Patient P125

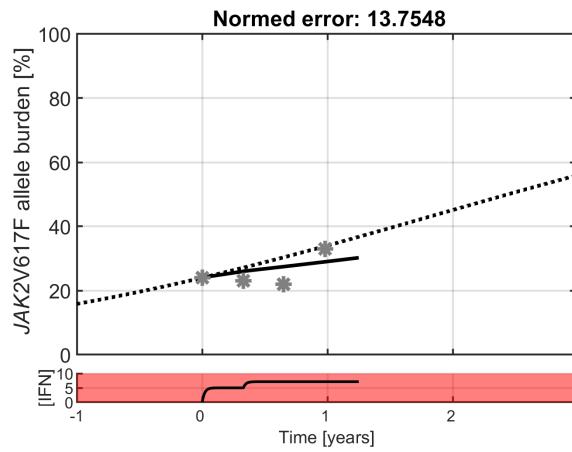
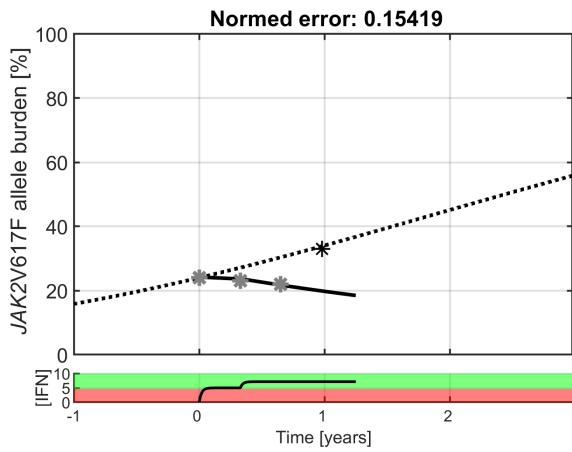


Patient P129

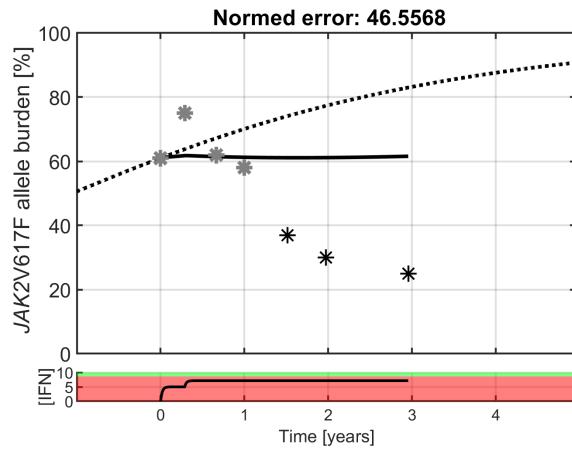
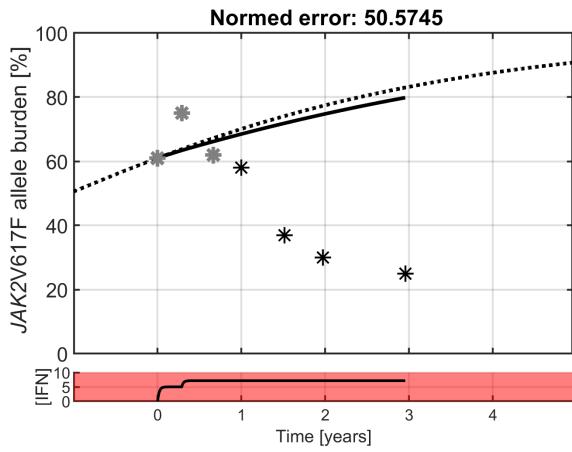


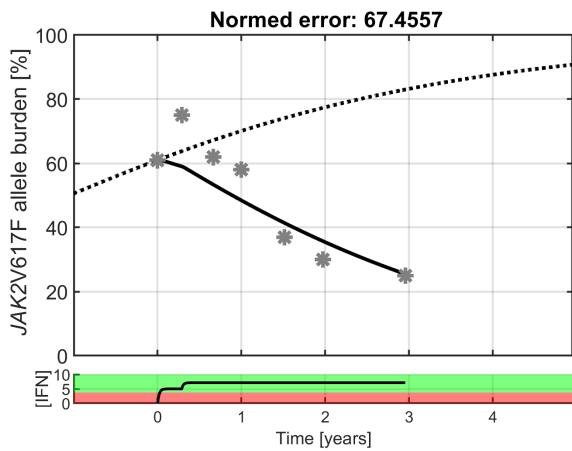
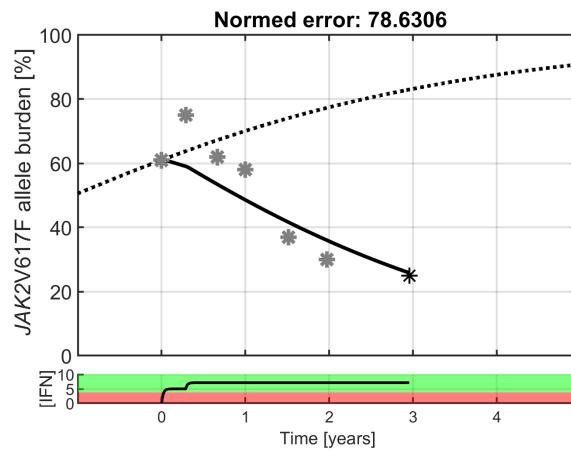
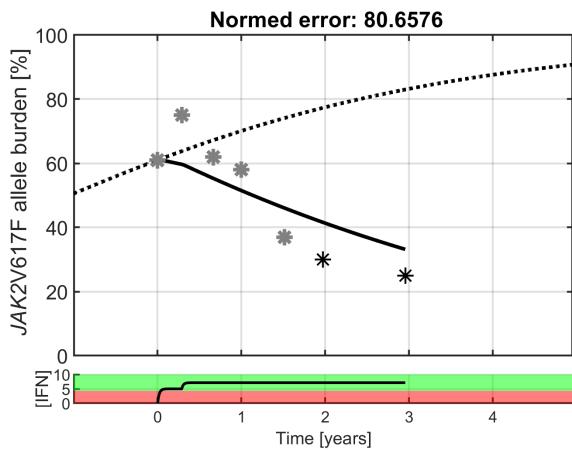


Patient P131

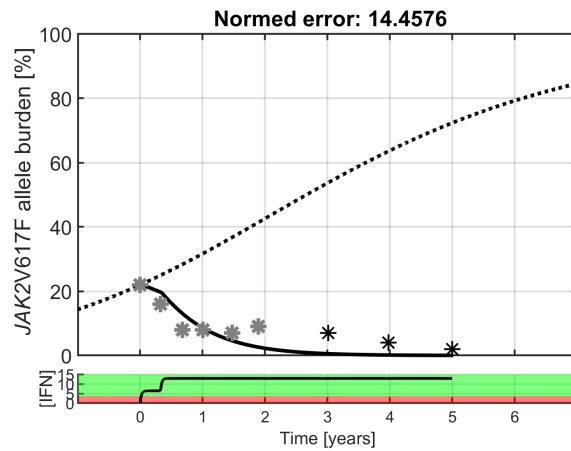
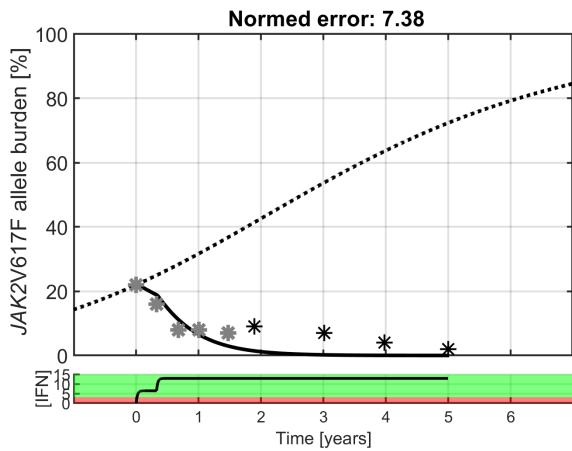
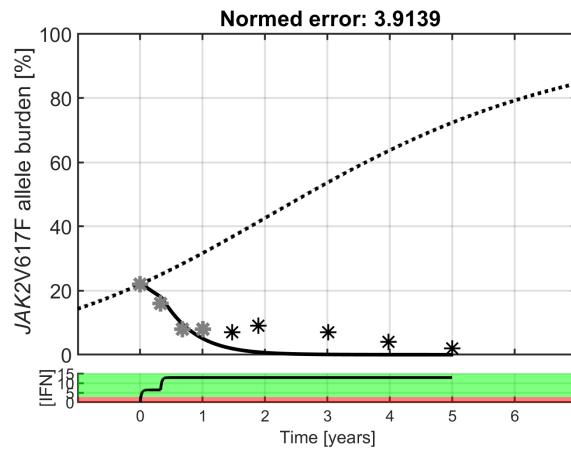
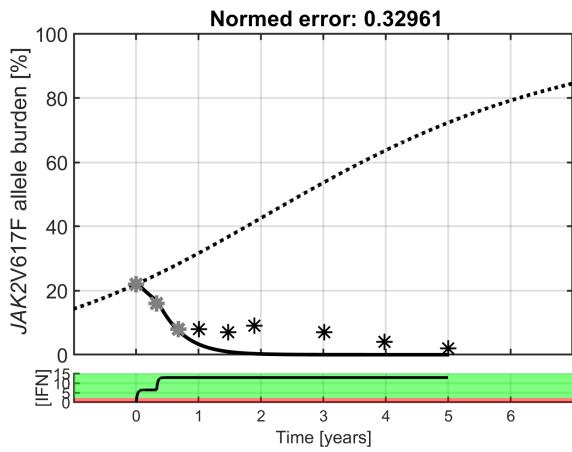


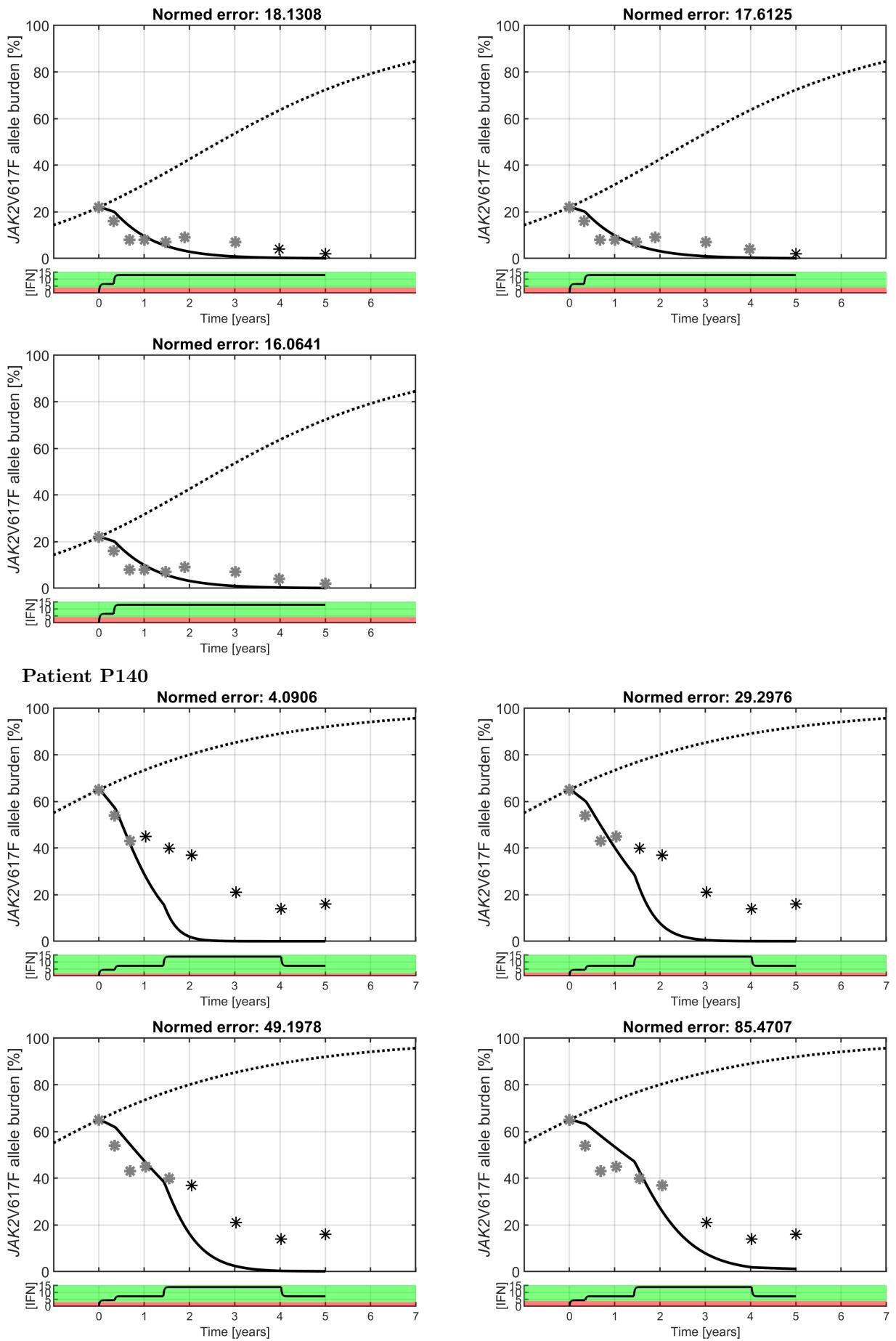
Patient P135

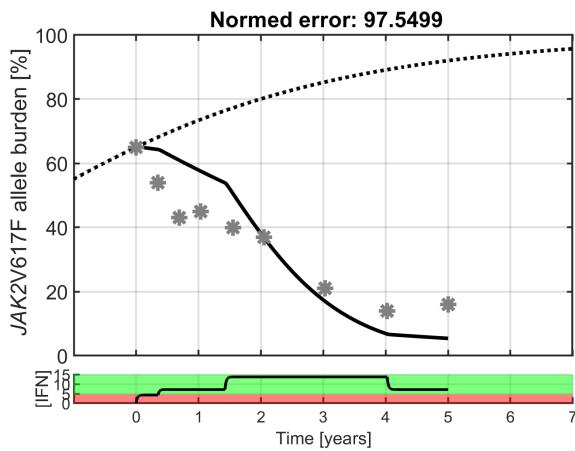
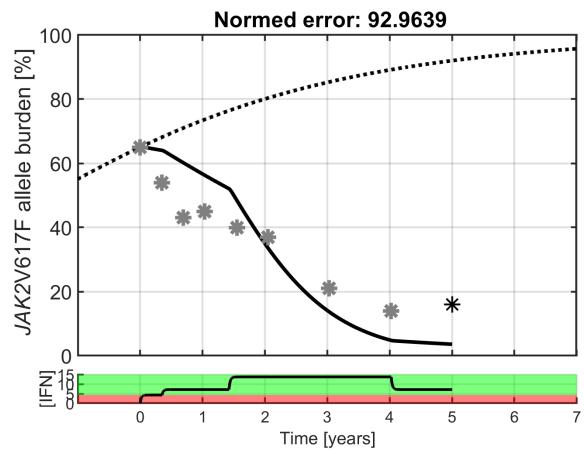
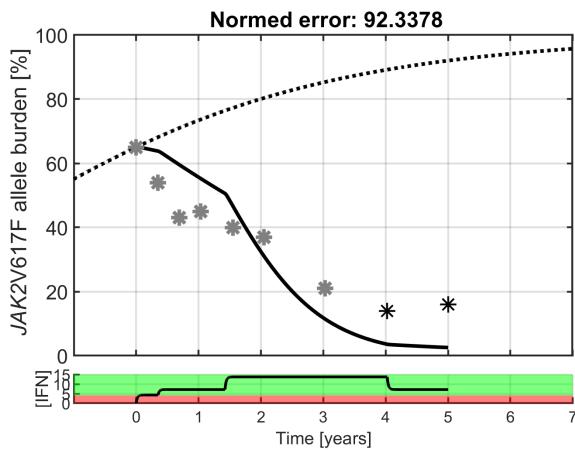




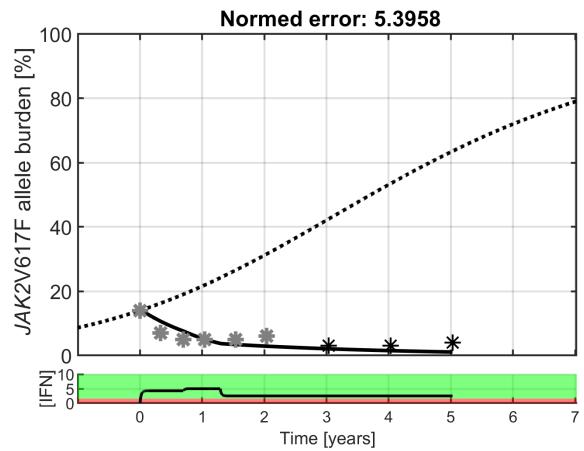
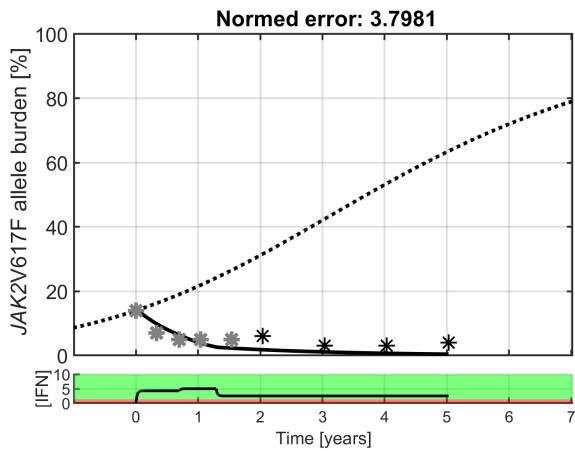
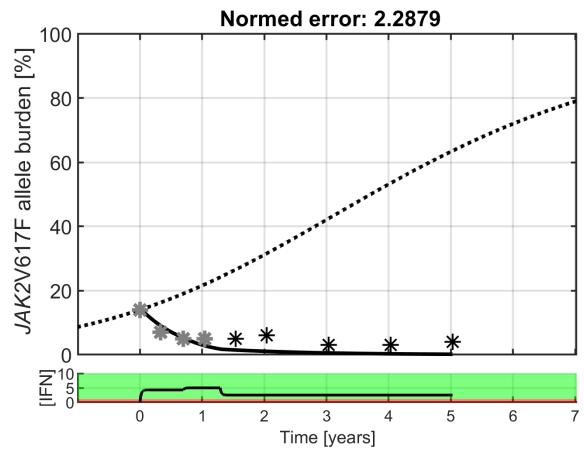
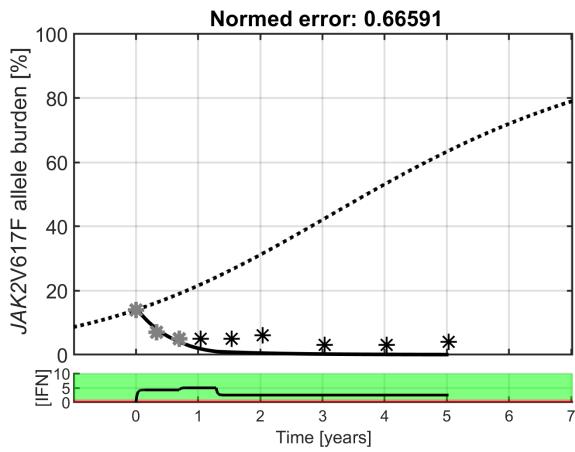
Patient P139

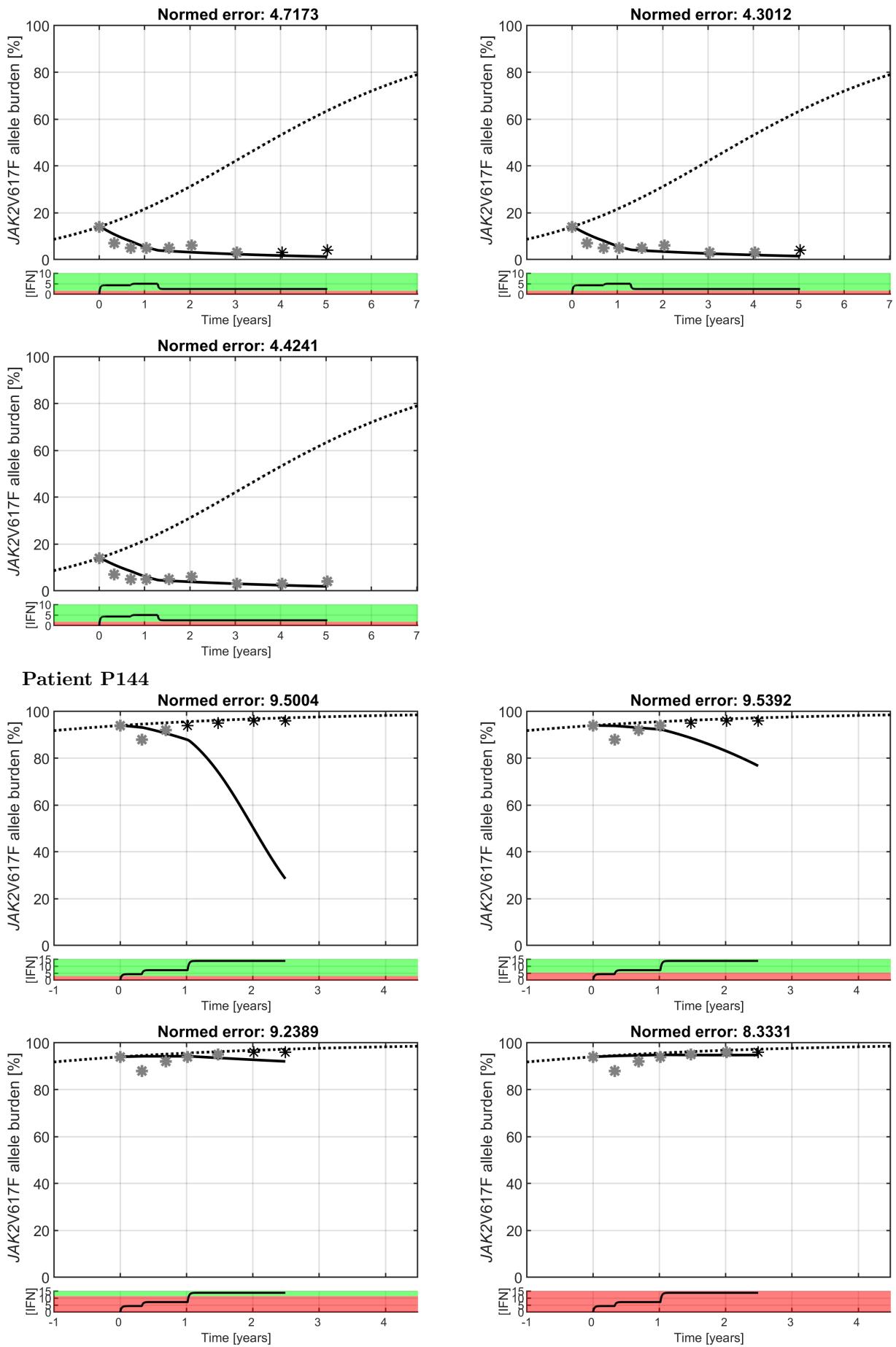


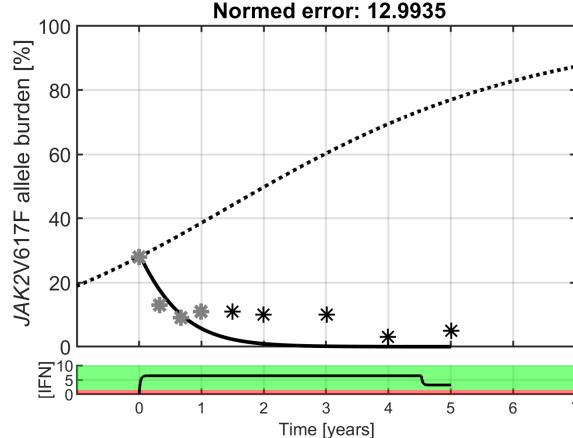
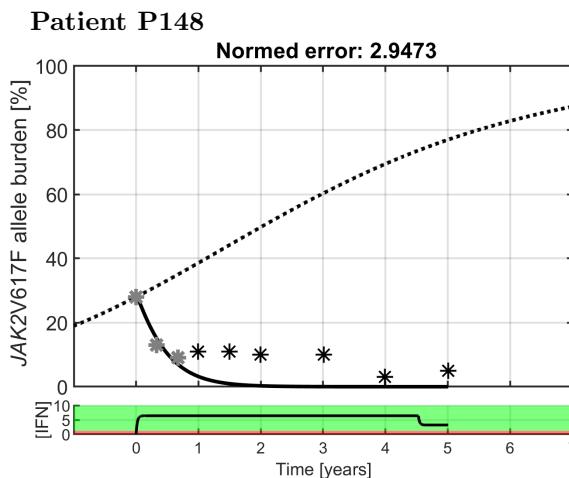
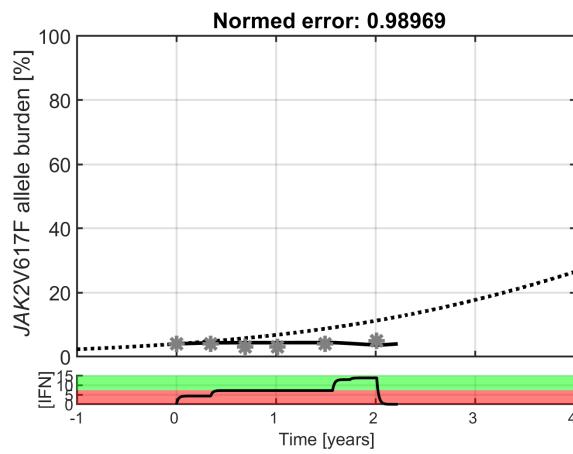
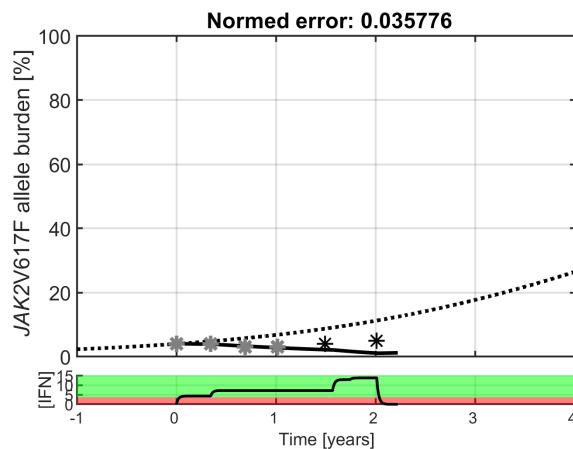
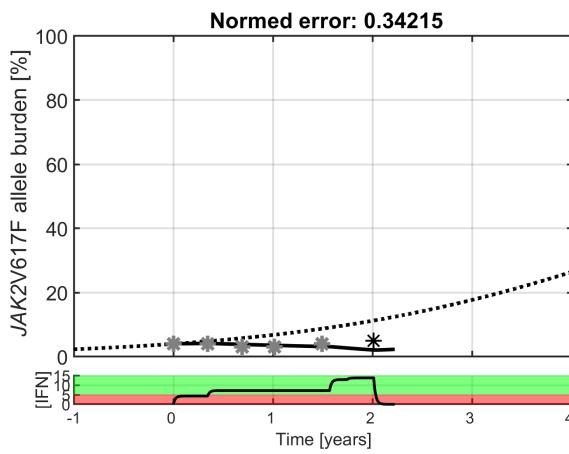
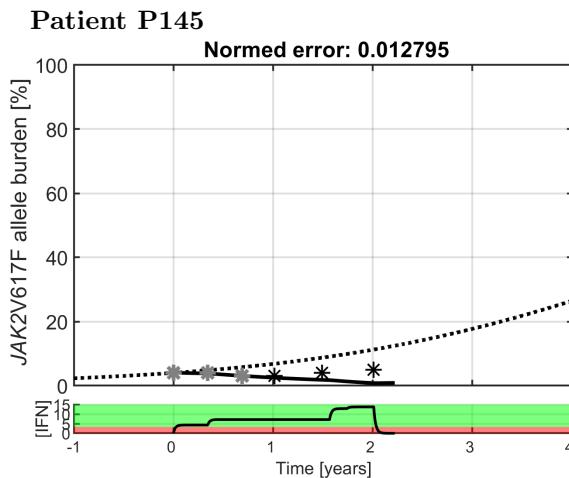
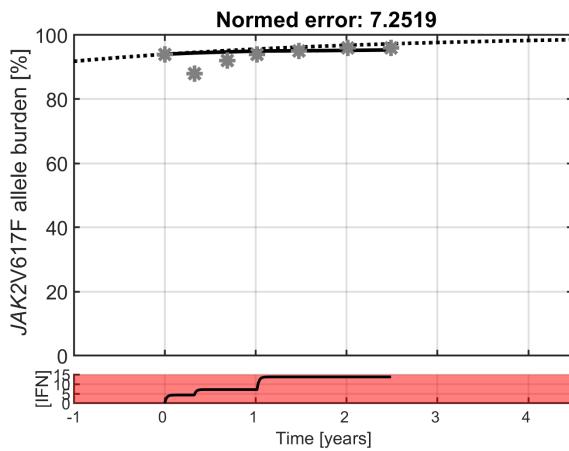


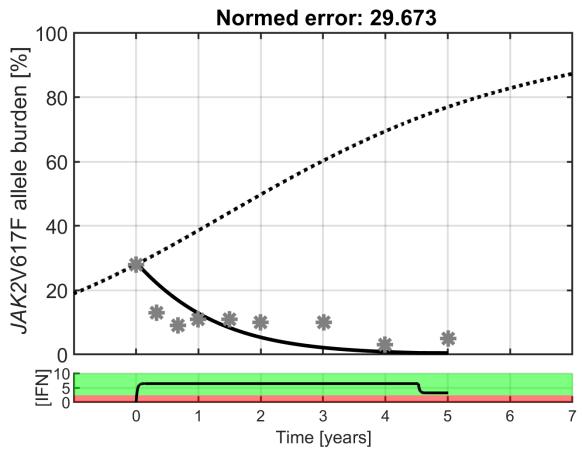
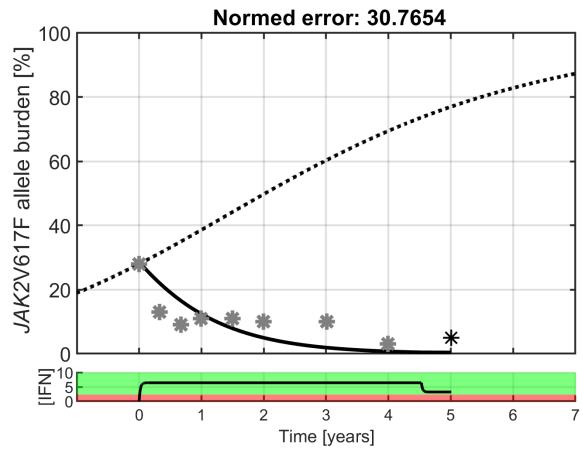
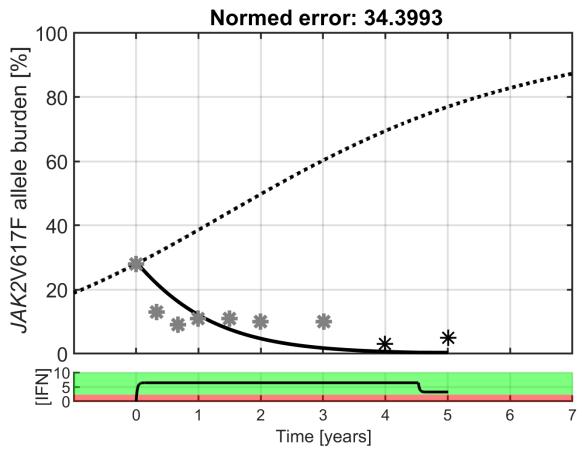
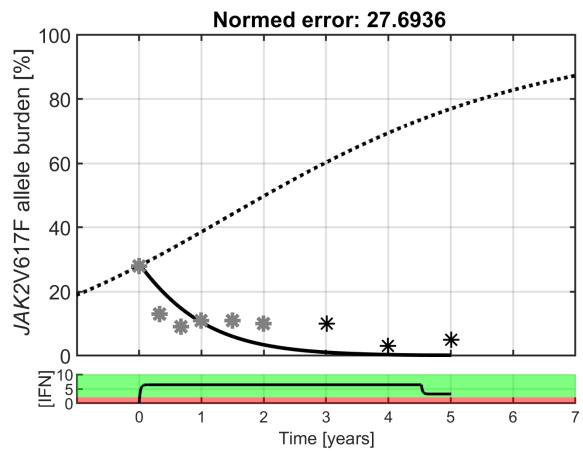
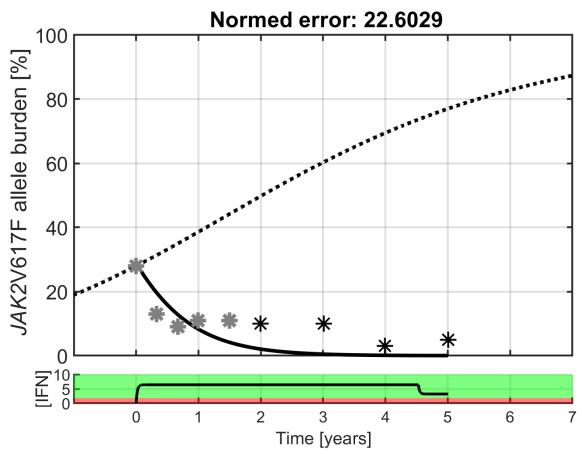


#### Patient P142

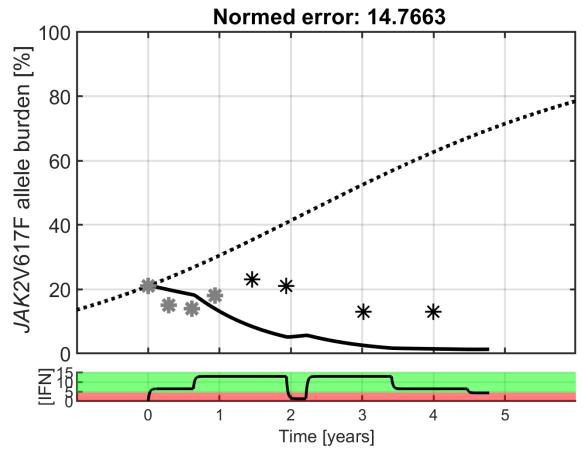
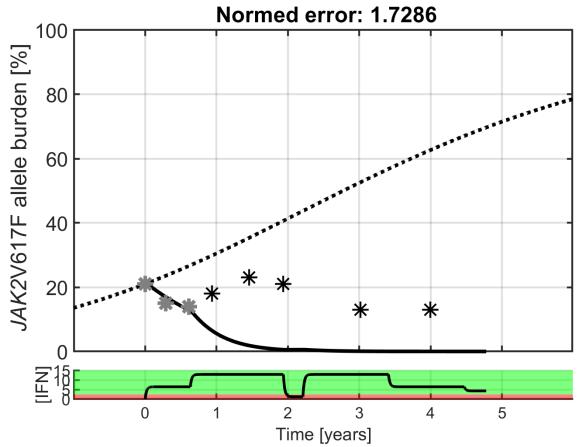


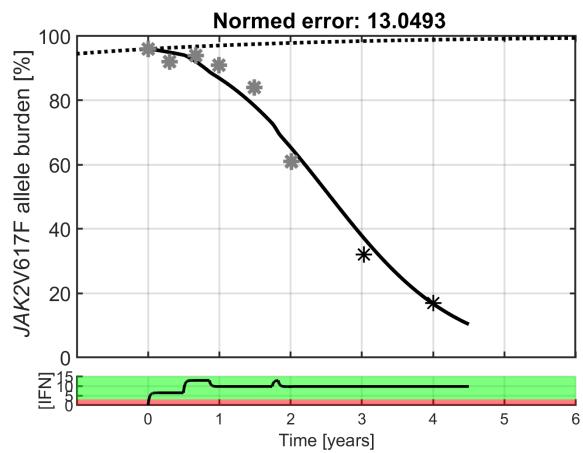
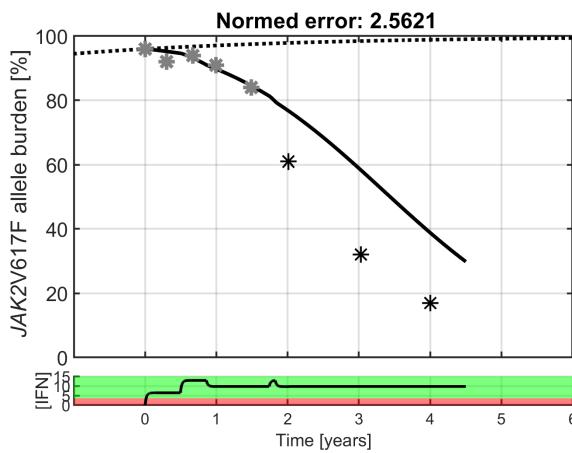
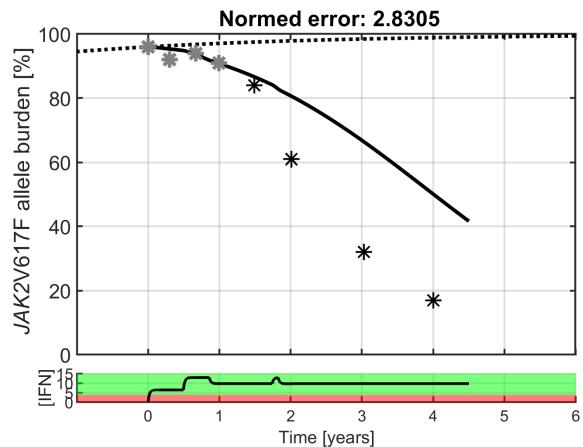
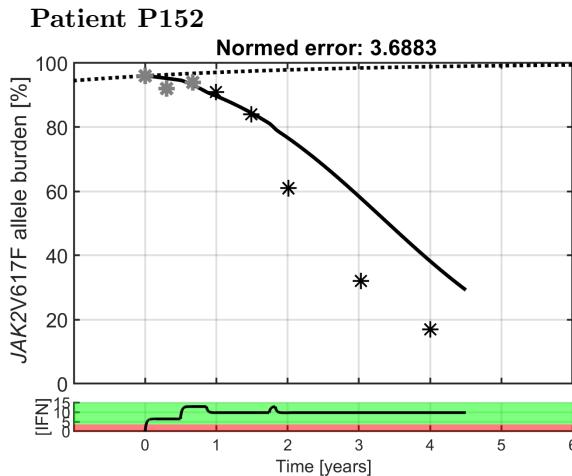
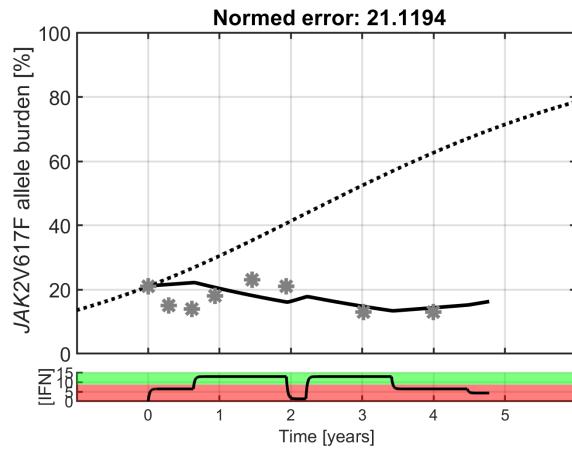
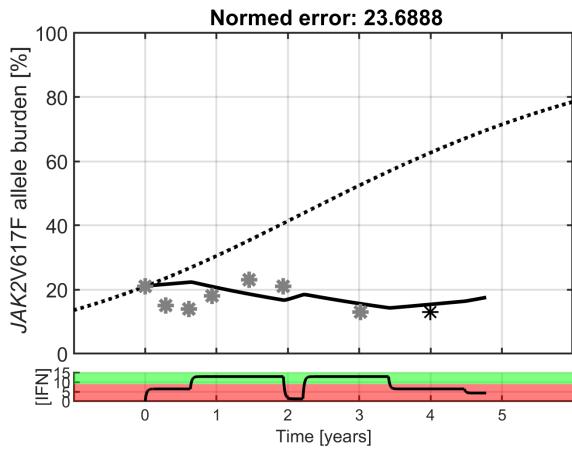
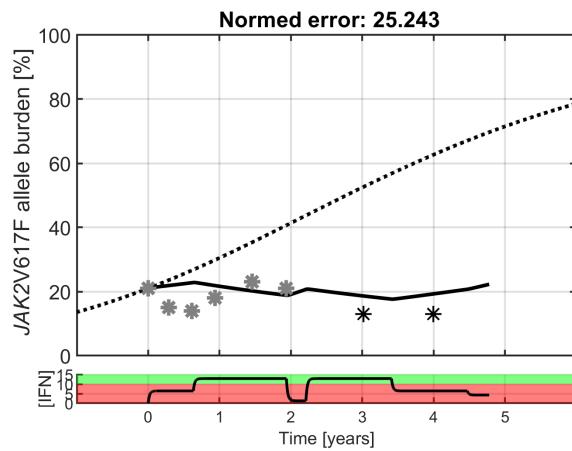
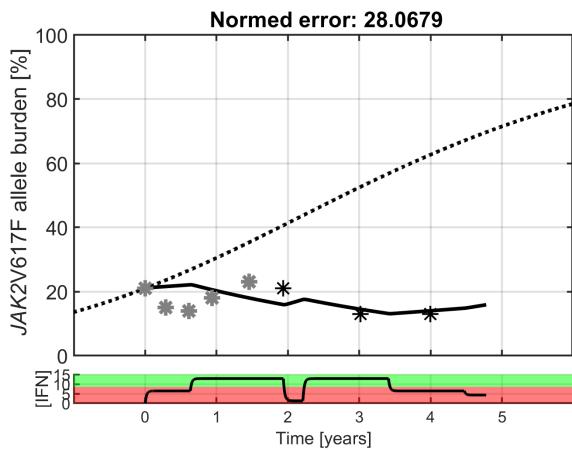


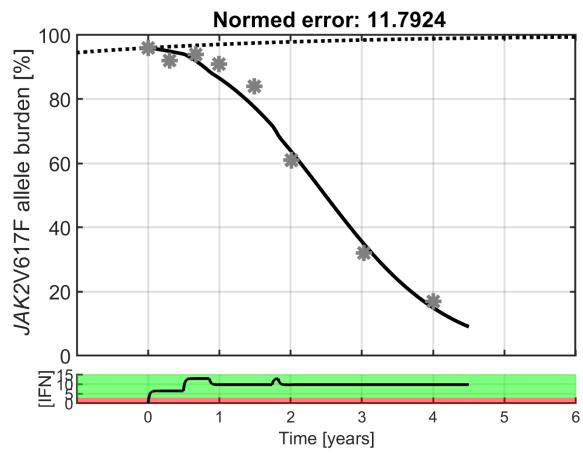
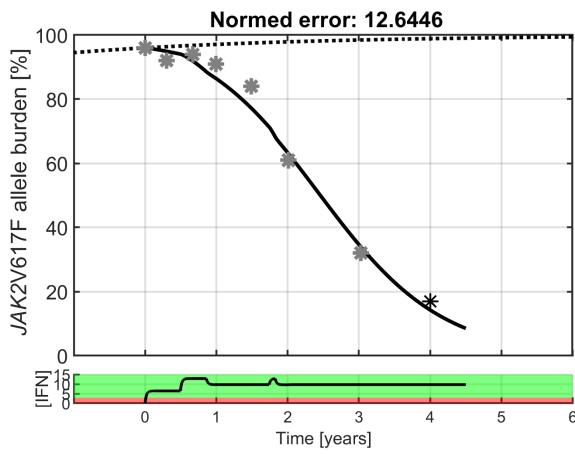




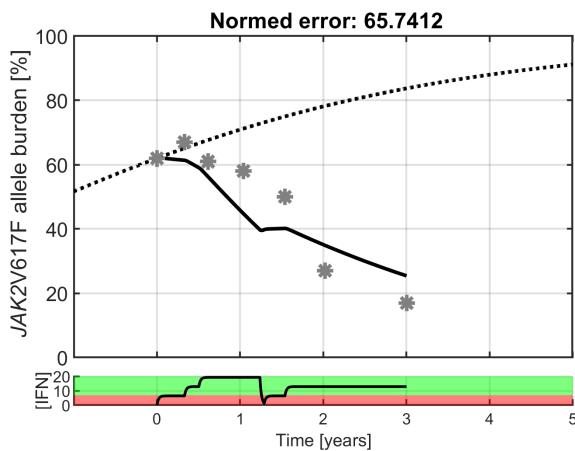
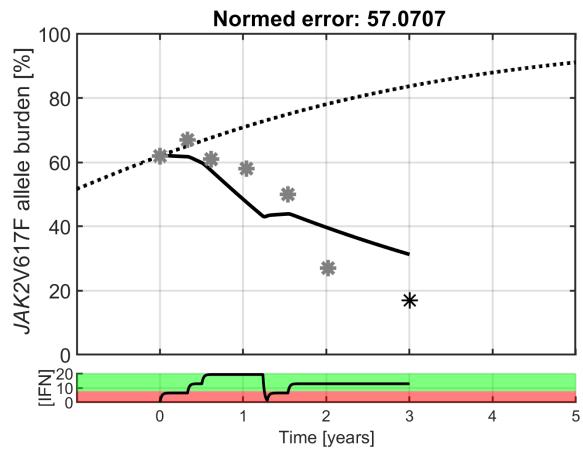
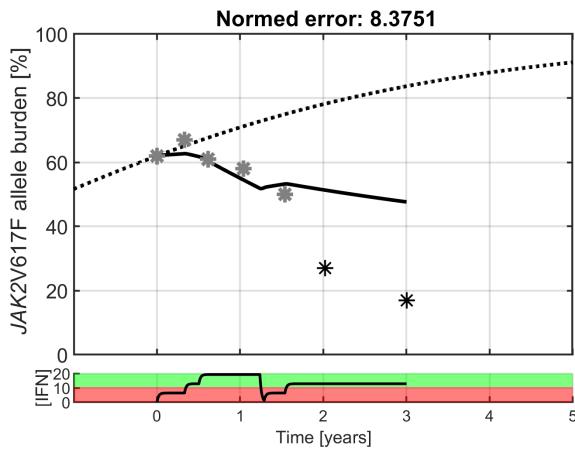
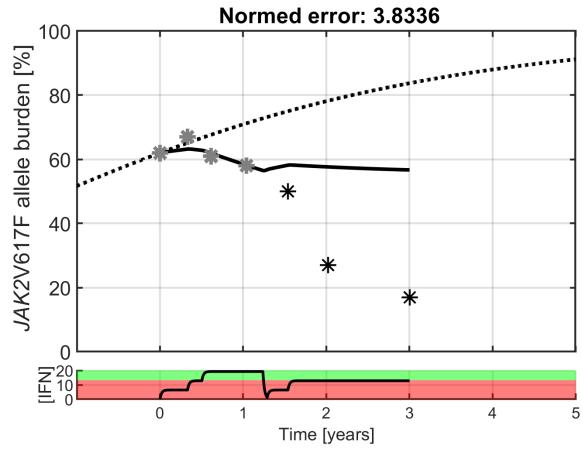
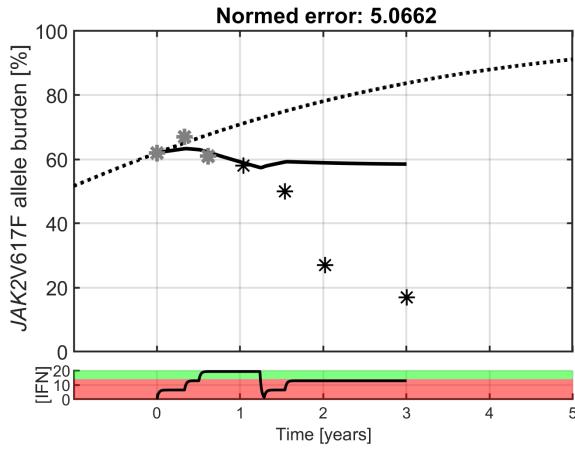
### Patient P150



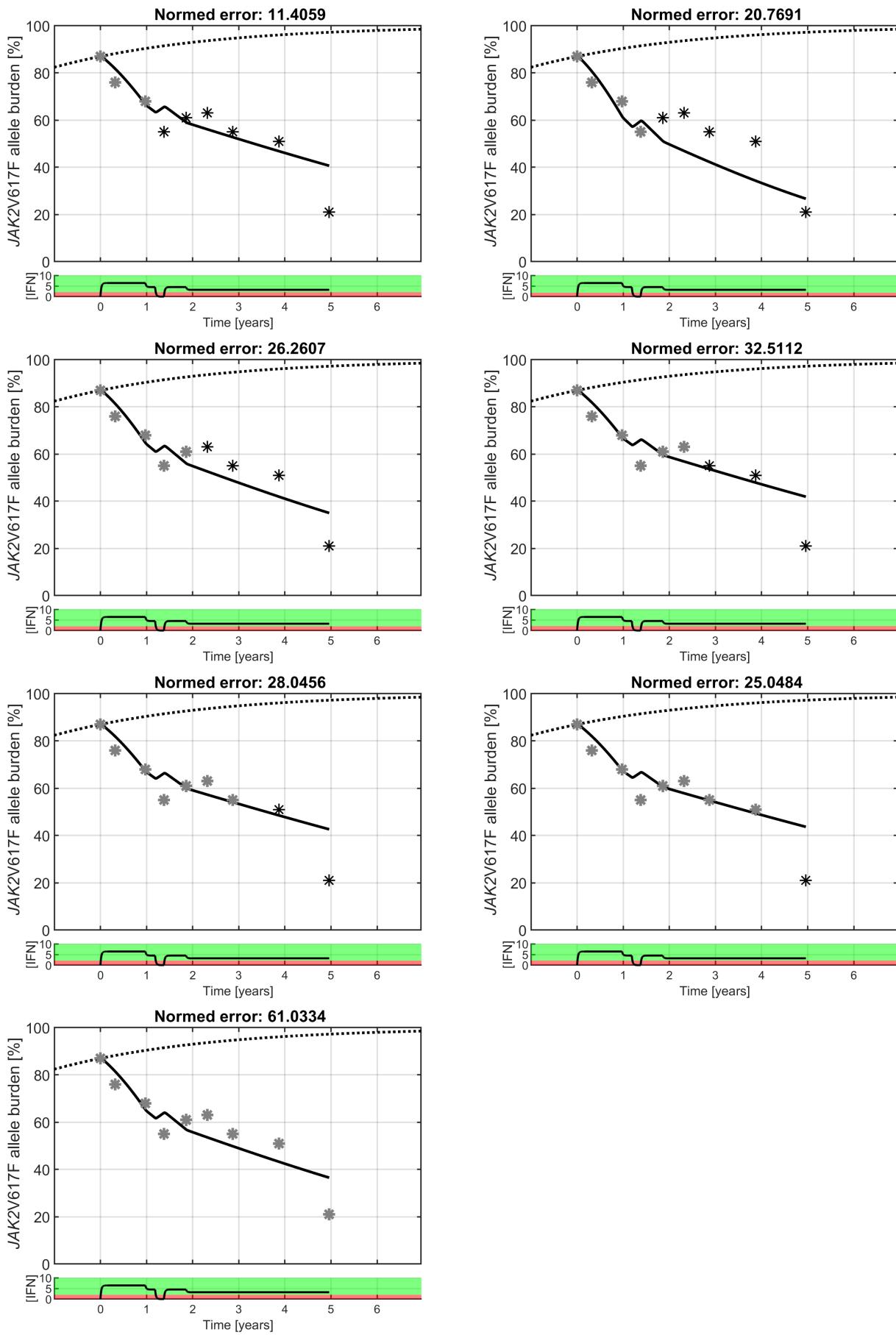


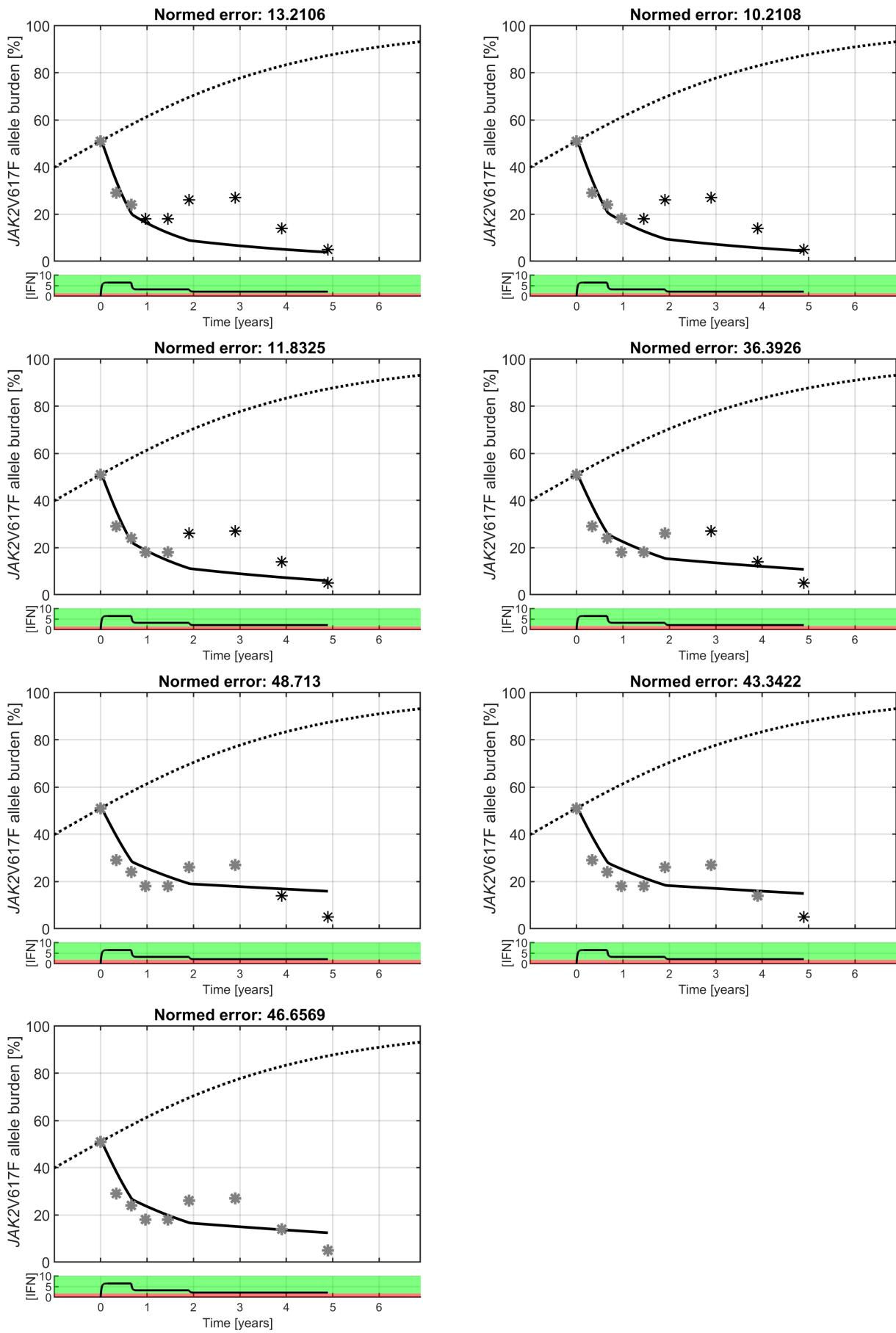


**Patient P156**

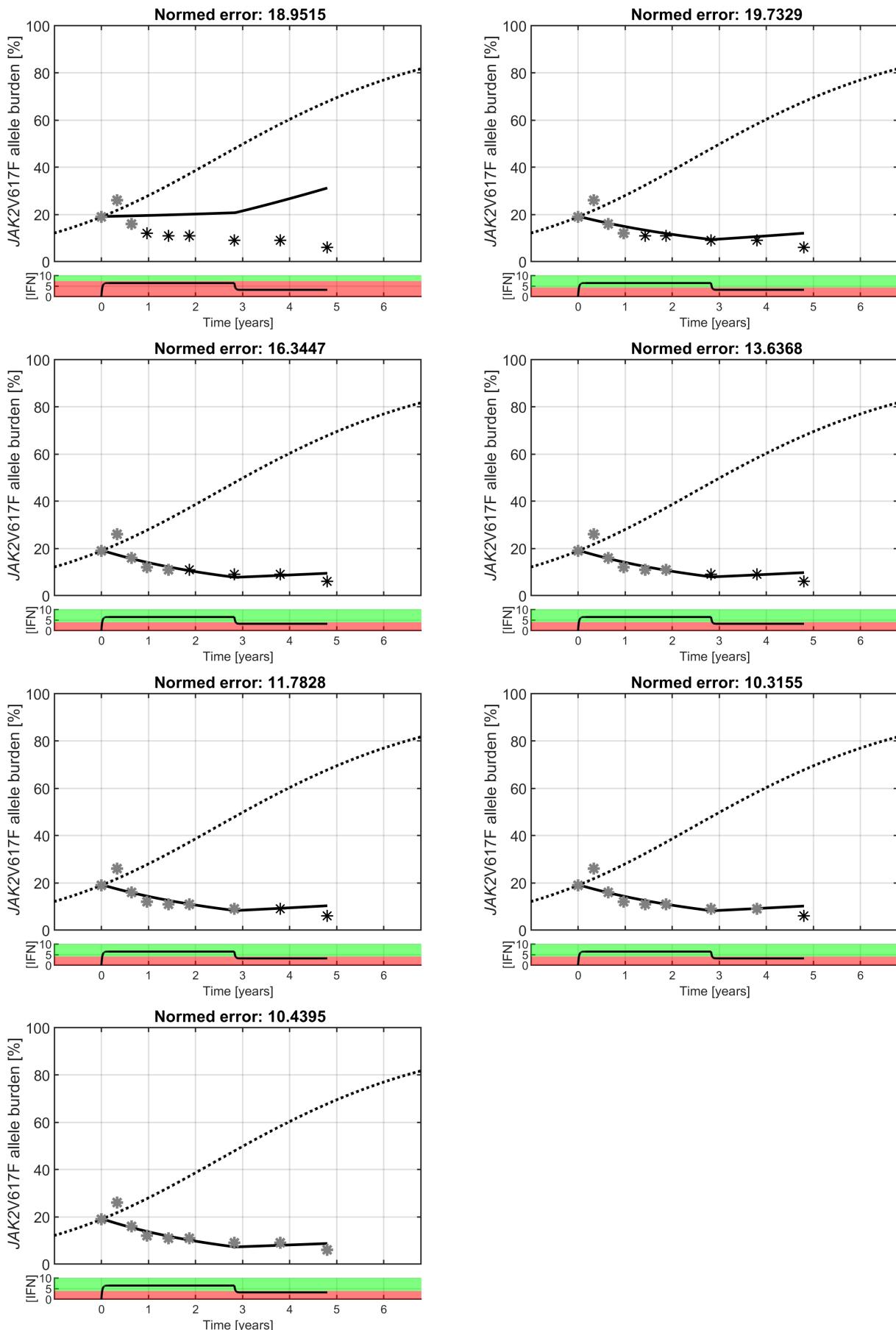


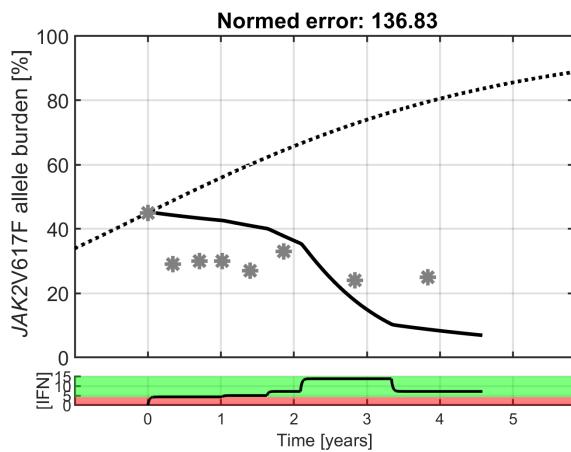
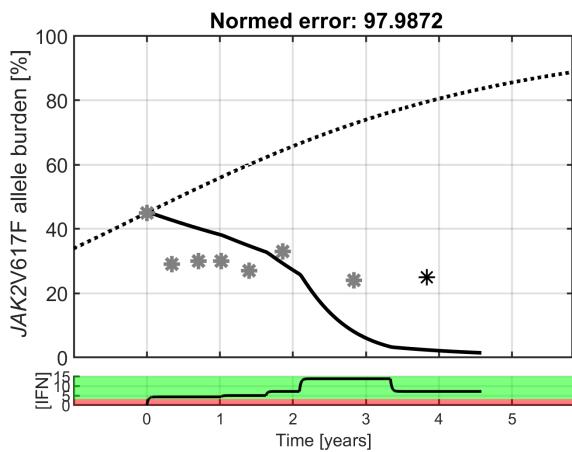
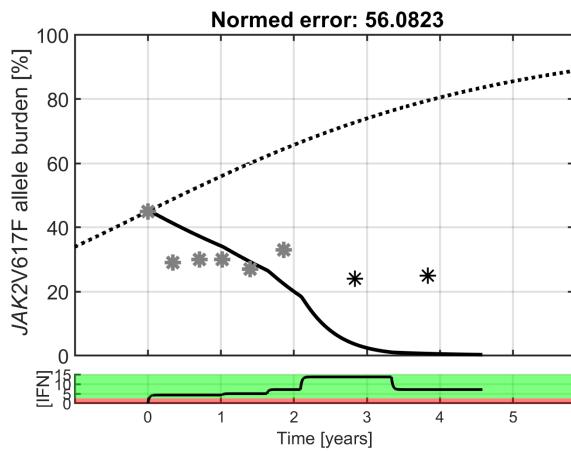
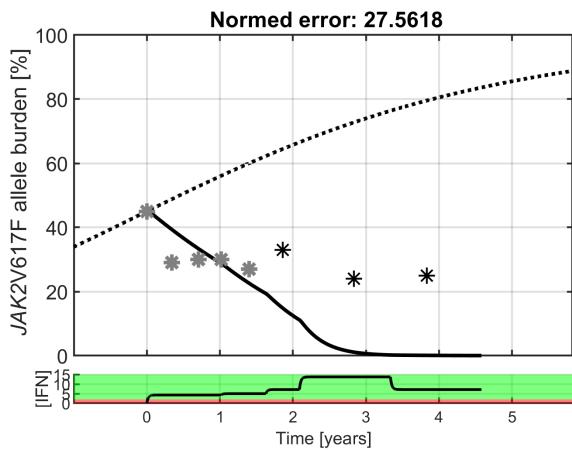
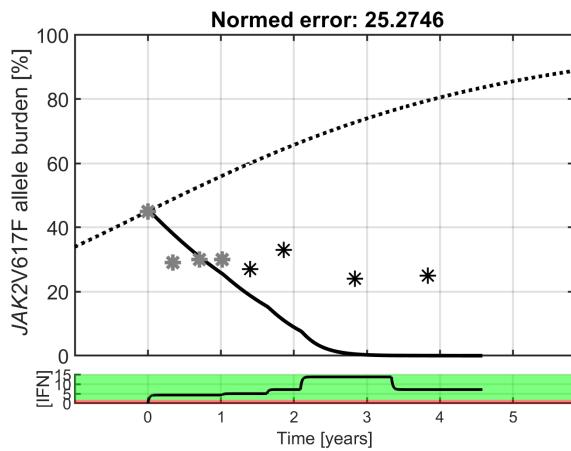
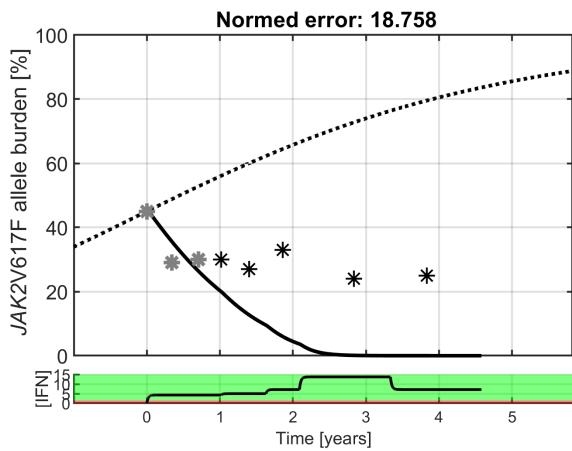
**Patient P158**



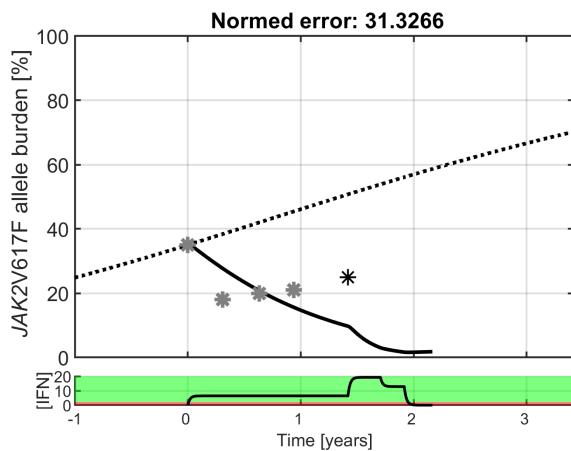
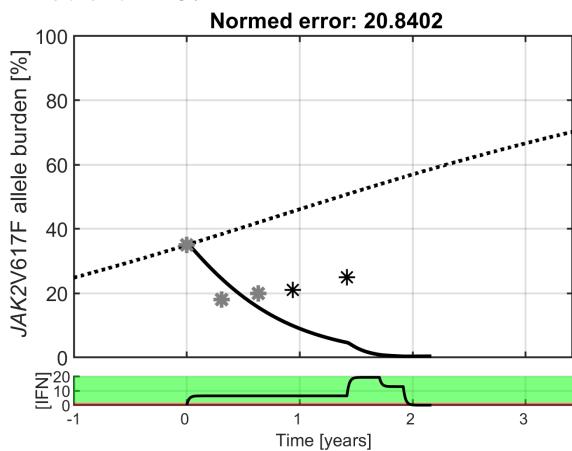


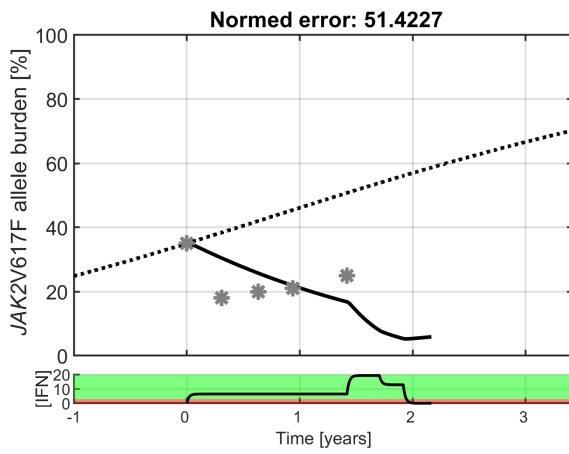
Patient P163



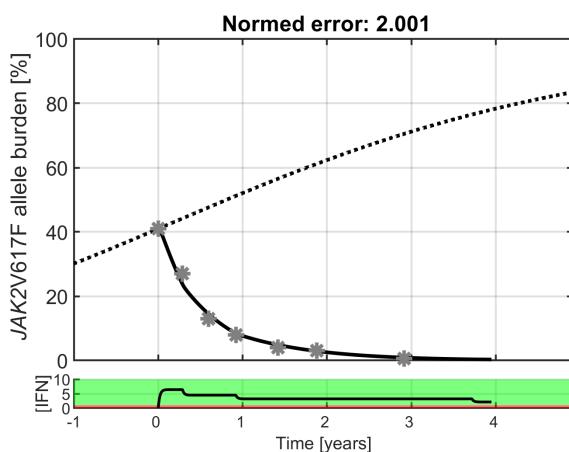
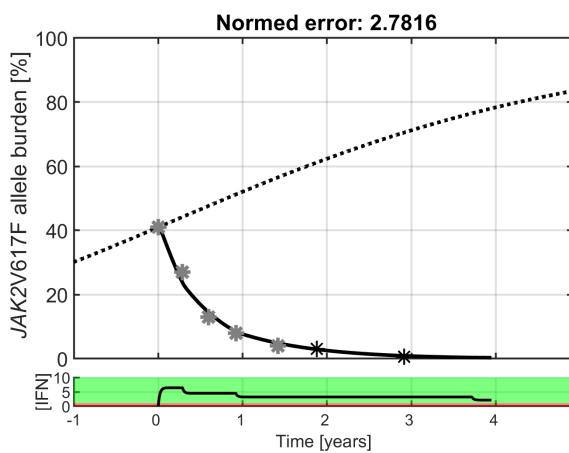
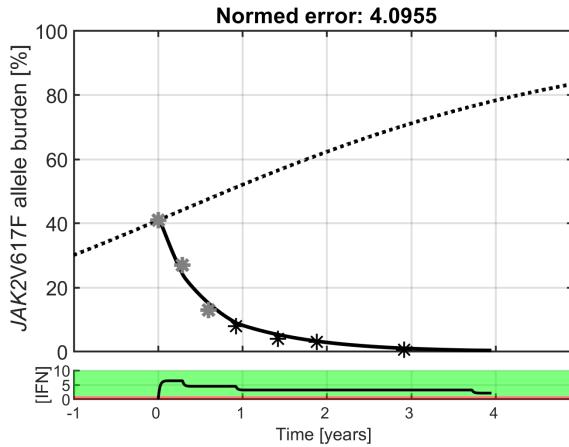


### Patient P167

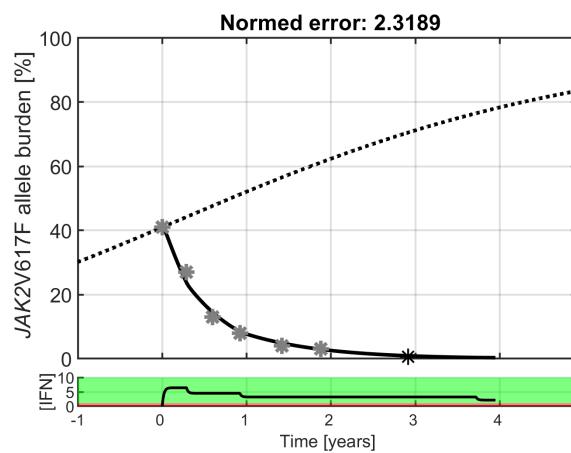
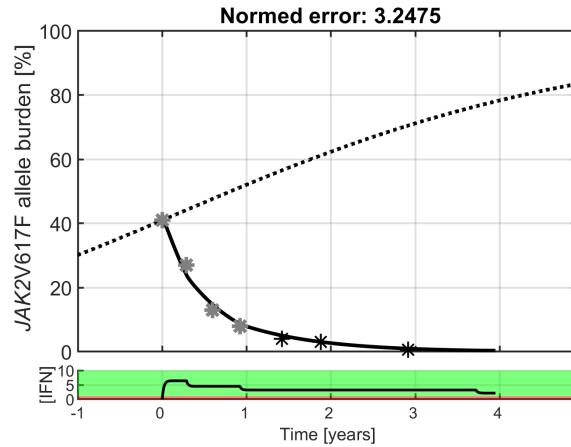


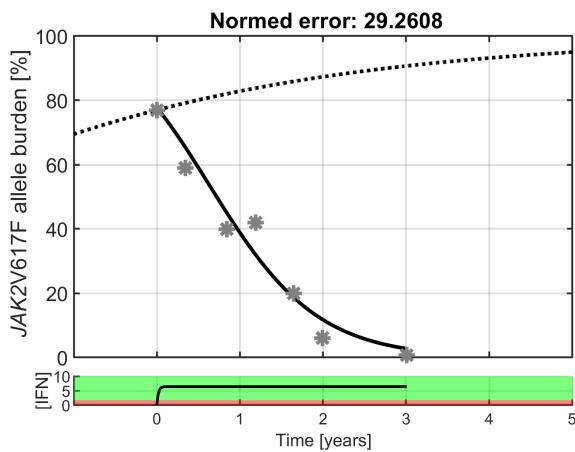
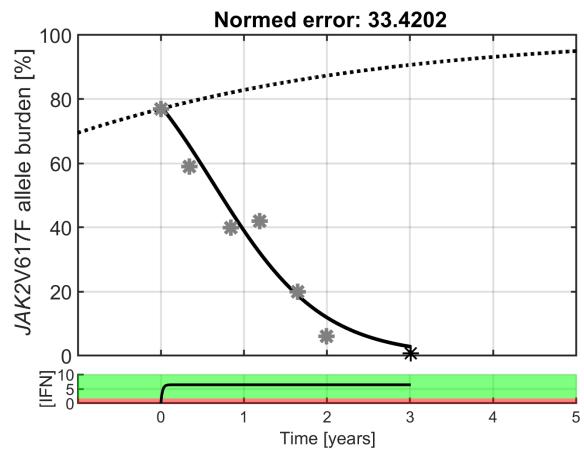
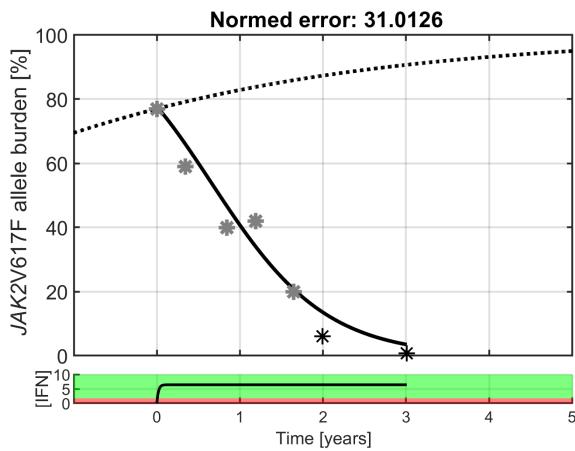
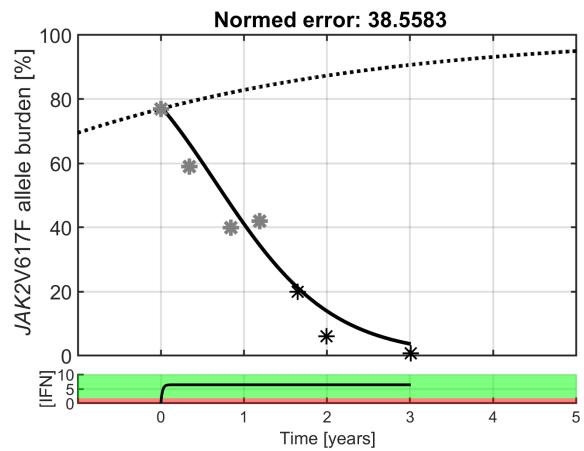
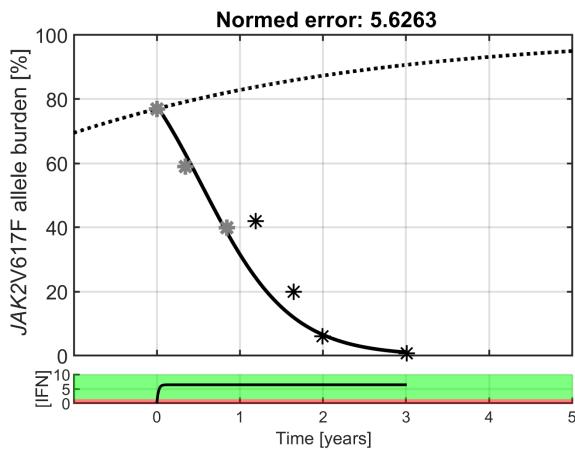


Patient P184

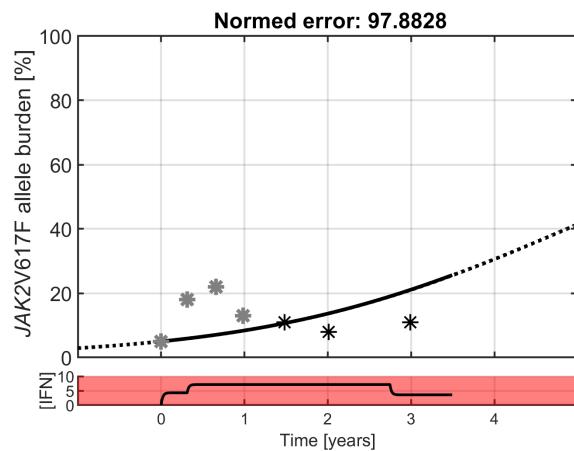
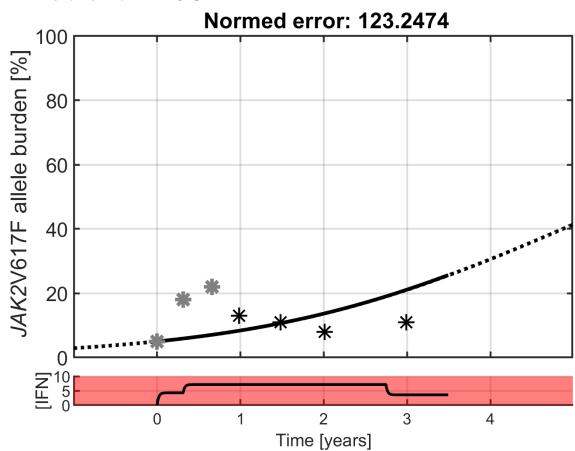


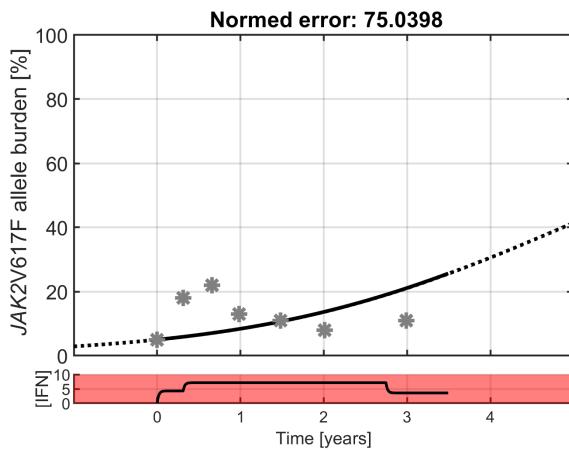
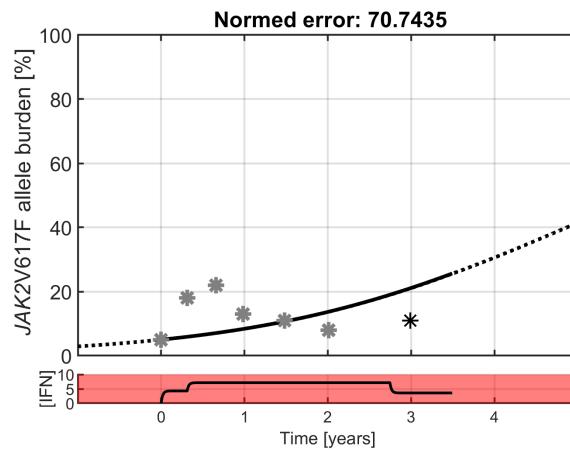
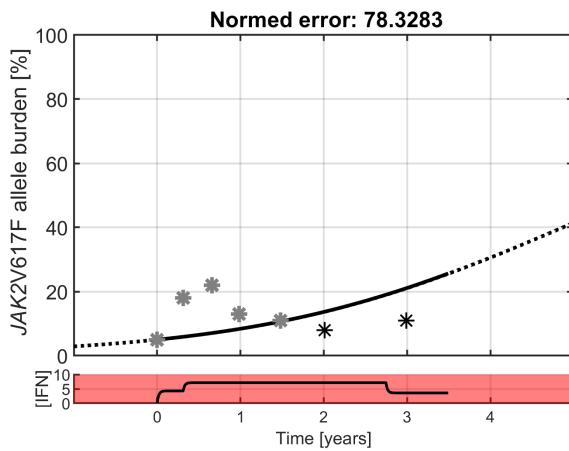
Patient P187



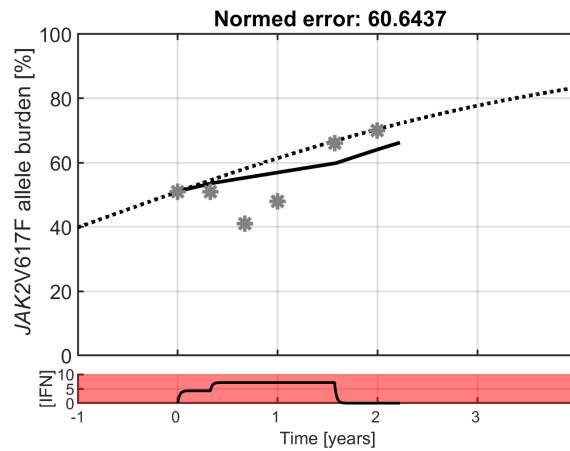
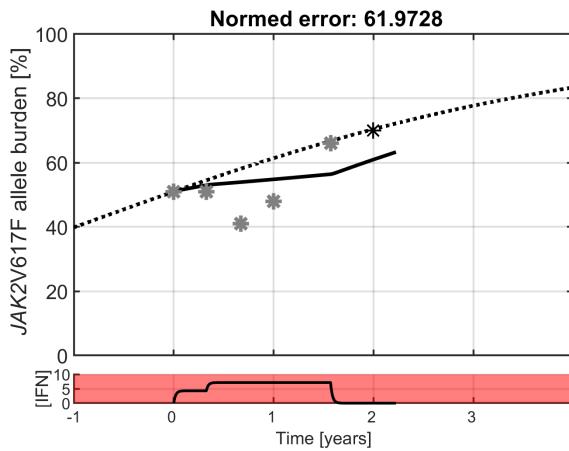
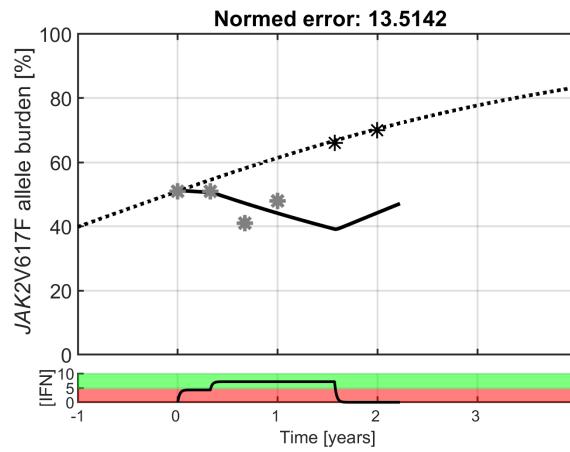
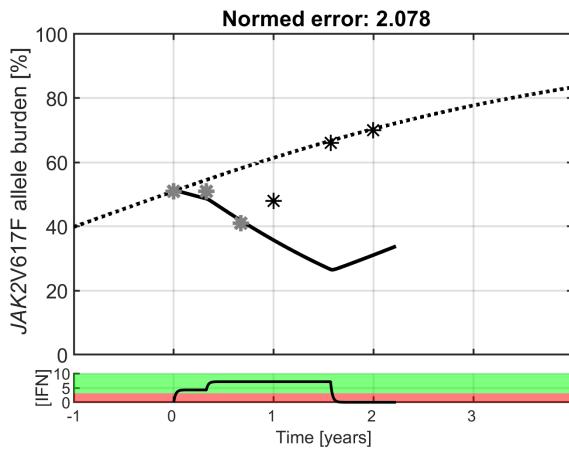


### Patient P190

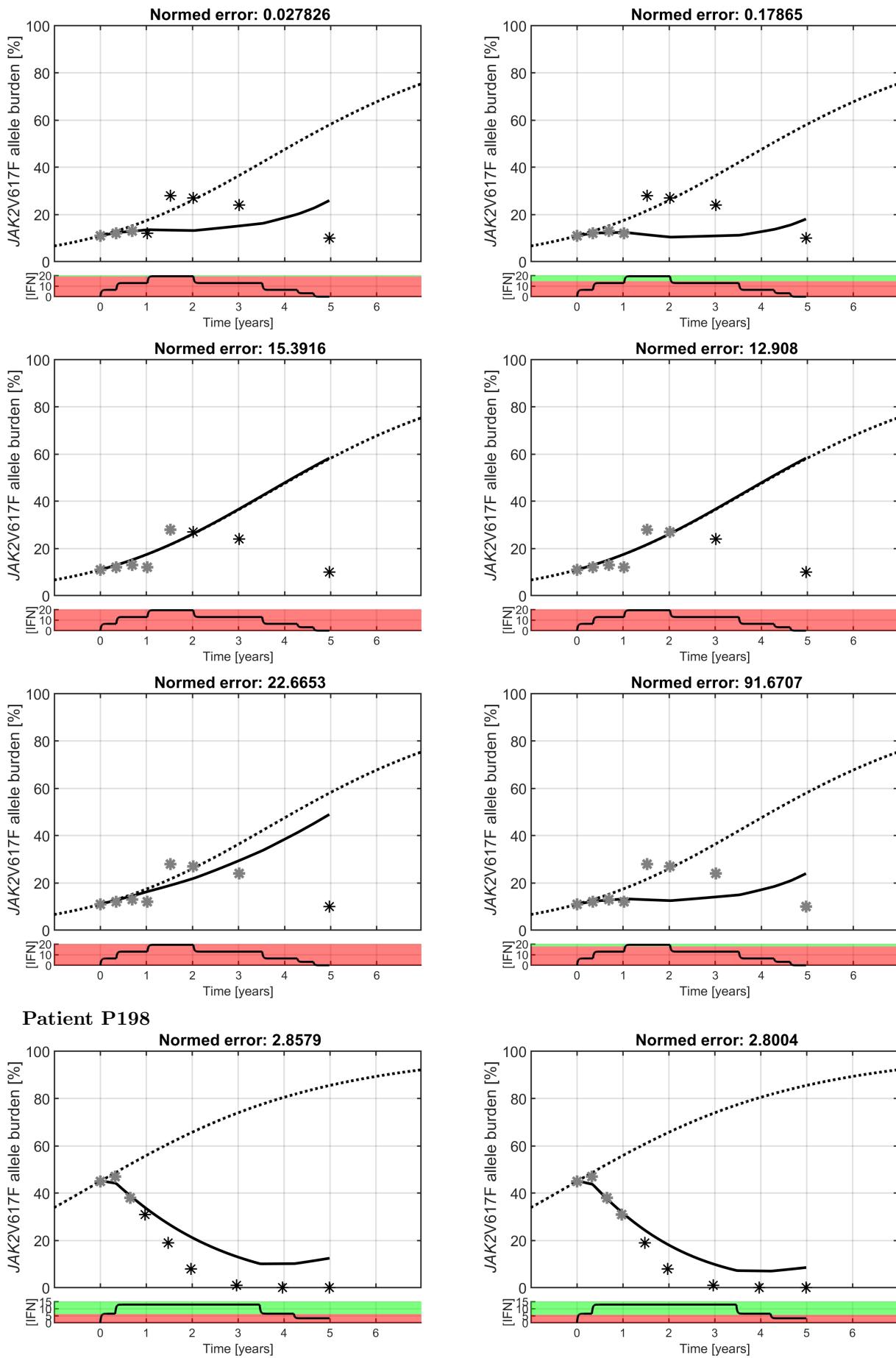


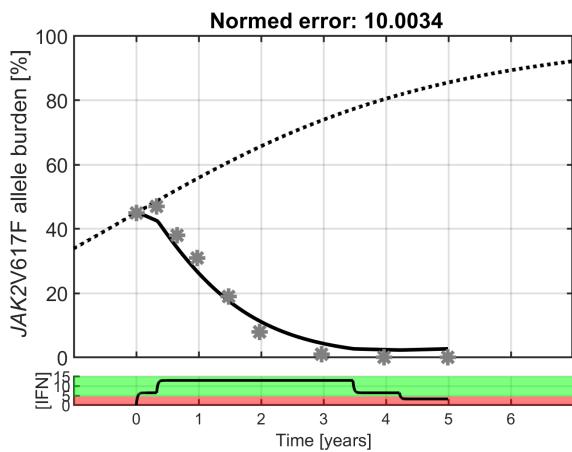
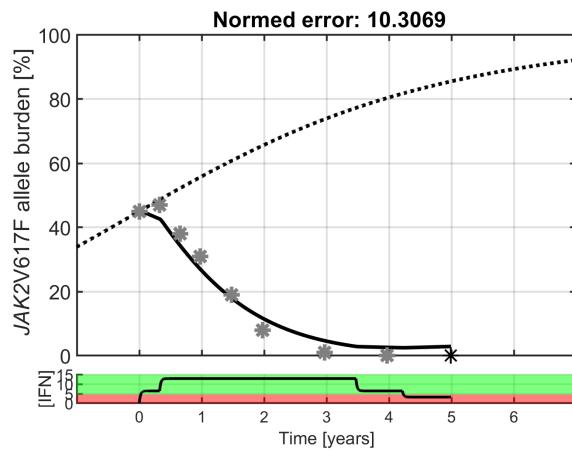
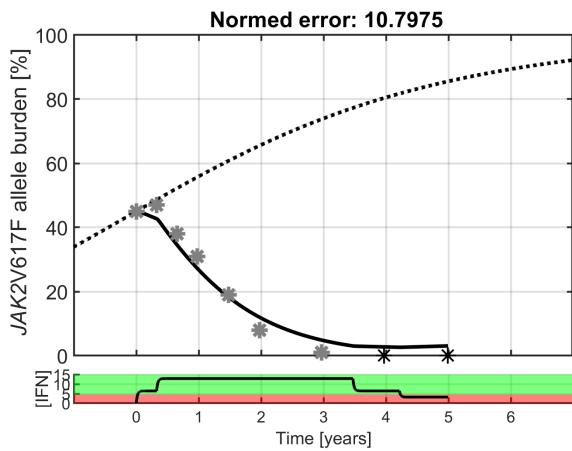
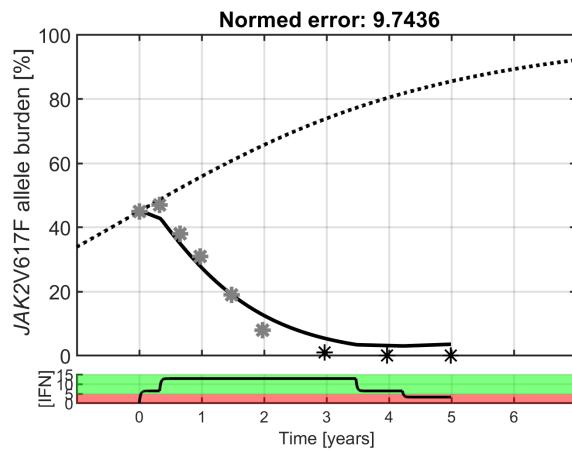
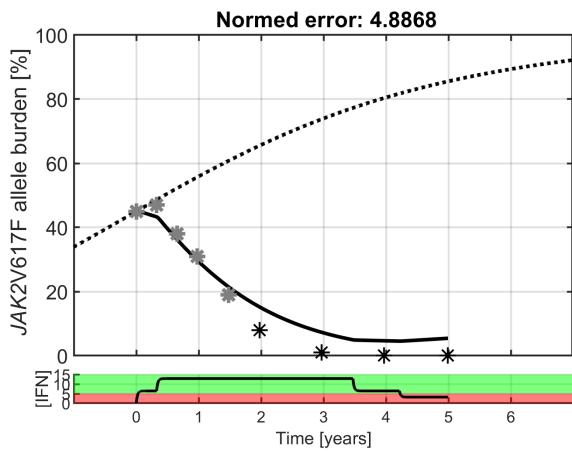


Patient P196

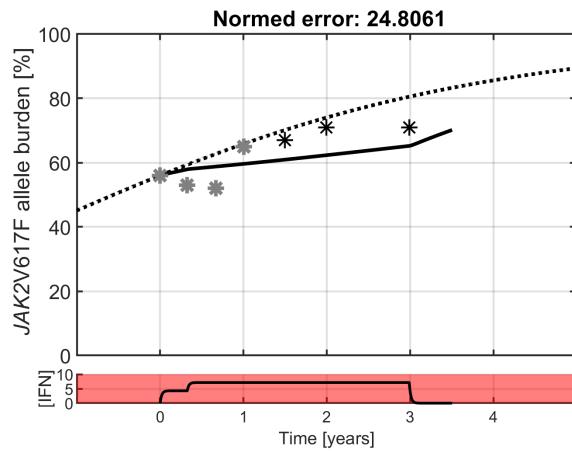
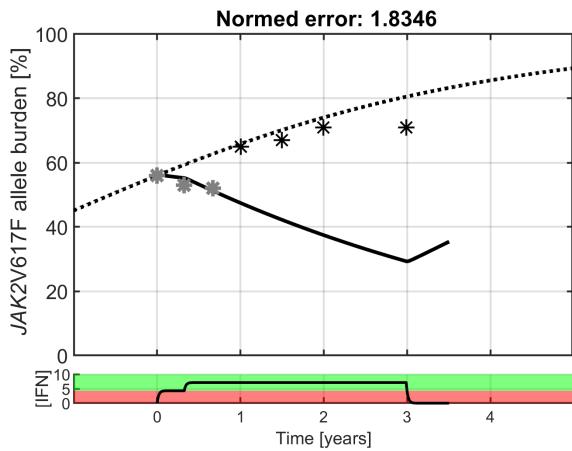


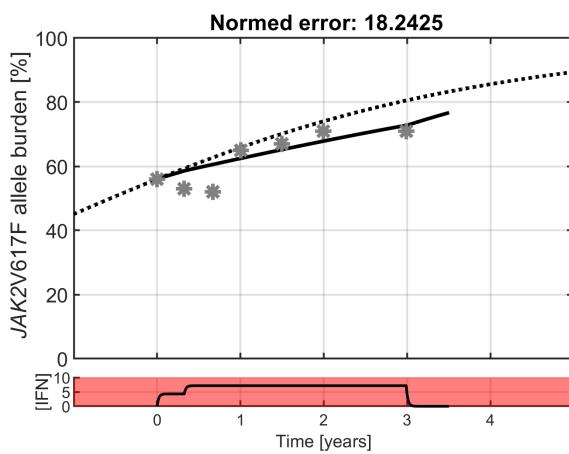
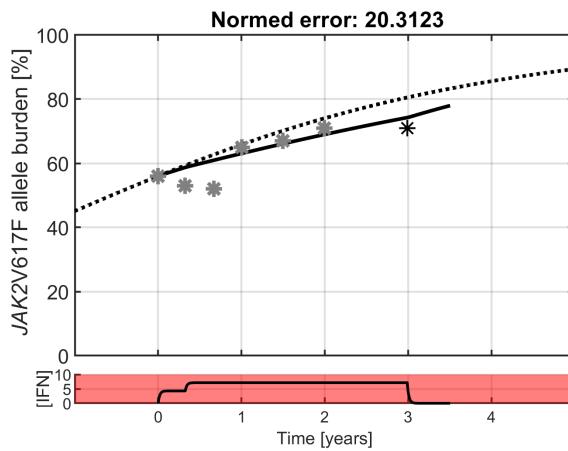
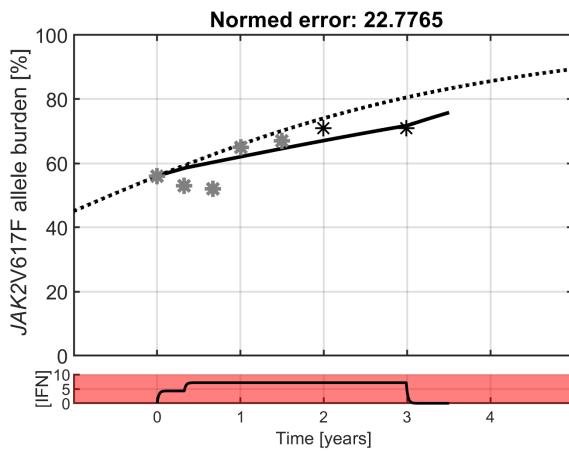
Patient P197



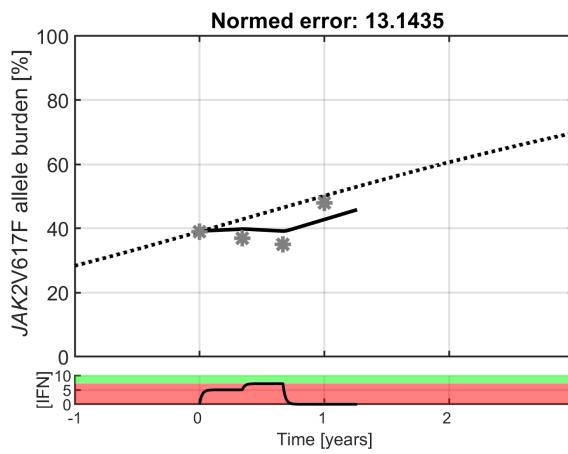
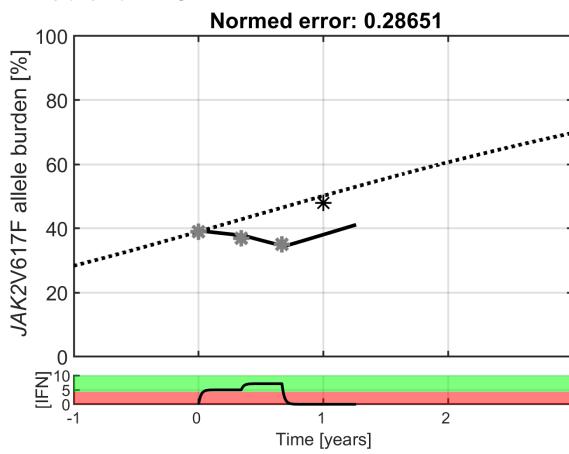


Patient P199

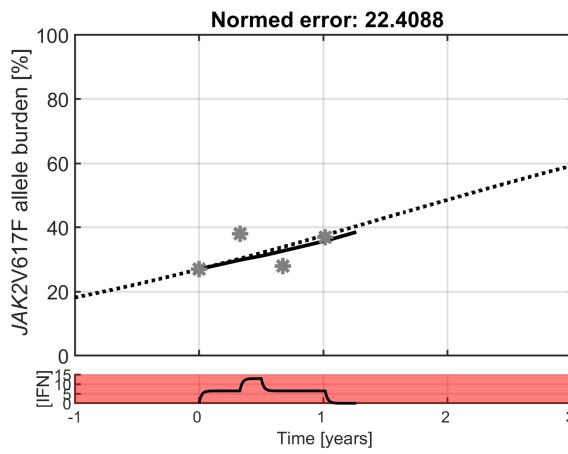
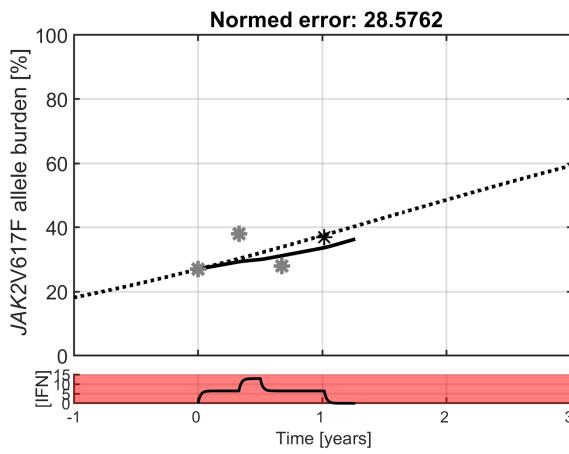




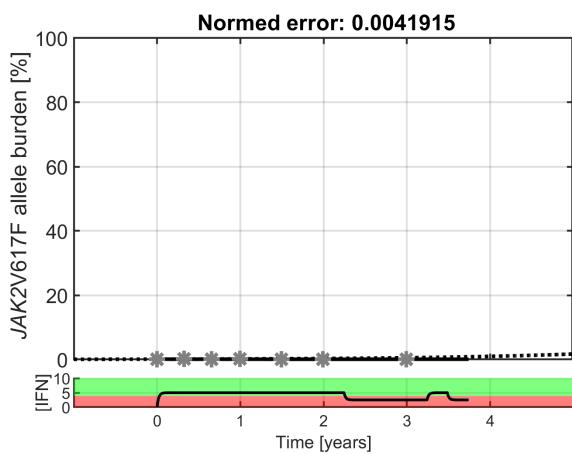
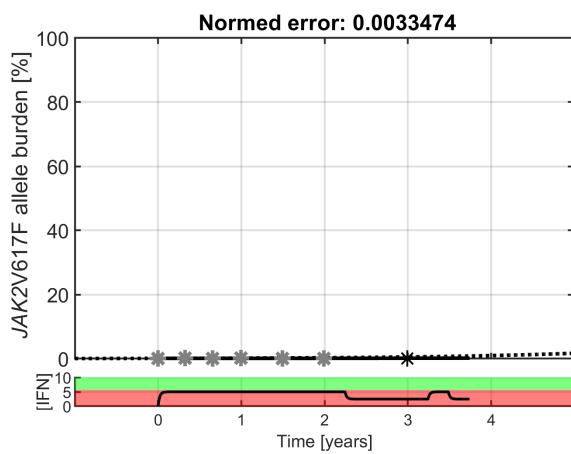
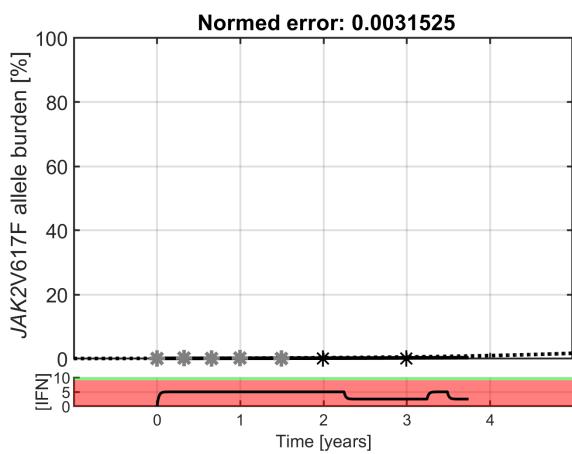
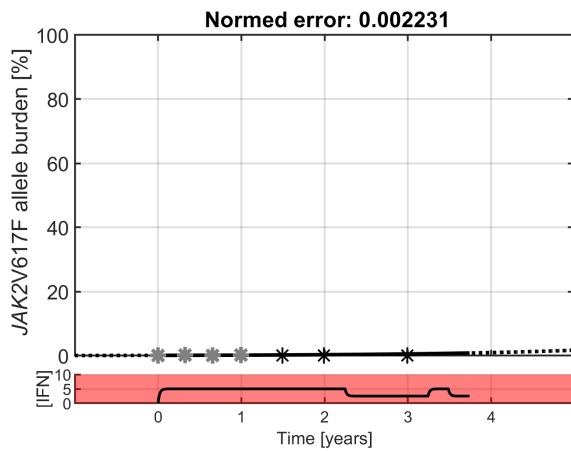
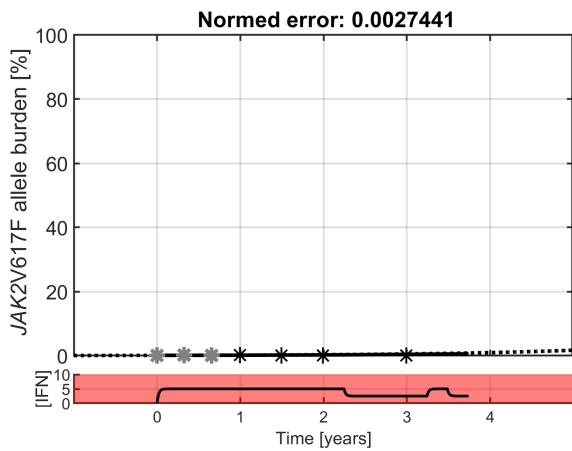
**Patient P201**



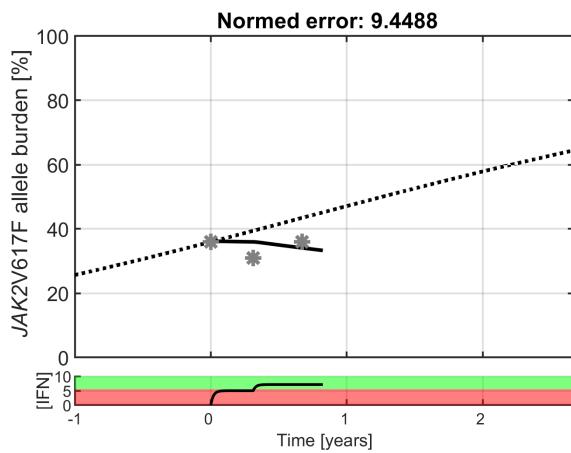
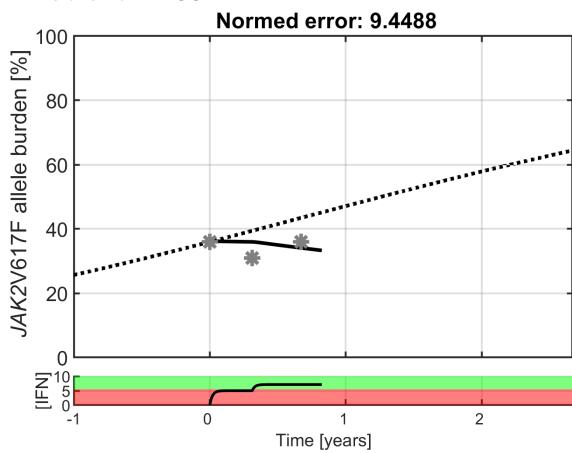
**Patient P202**



**Patient P203**



### Patient P205



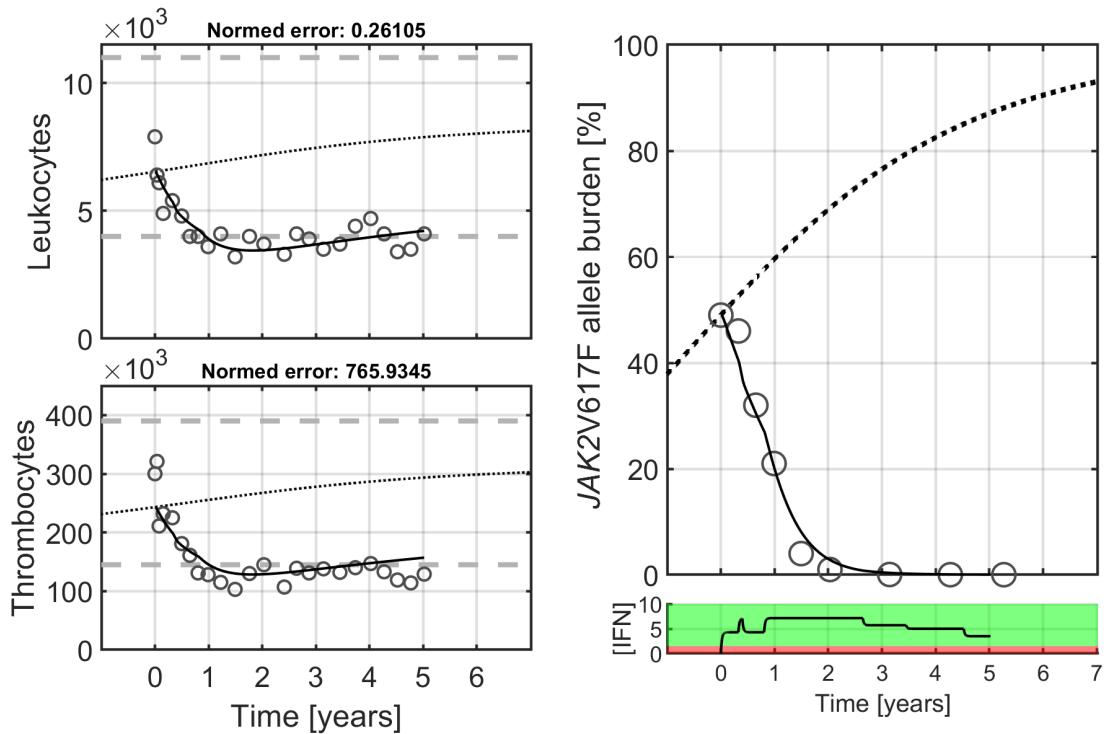
## Supplementary material C: Fits to leukocyte and thrombocyte data

Here we show the best fit to *JAK2V617F* allele burden, along with the subsequent fits to leukocytes and thrombocytes.

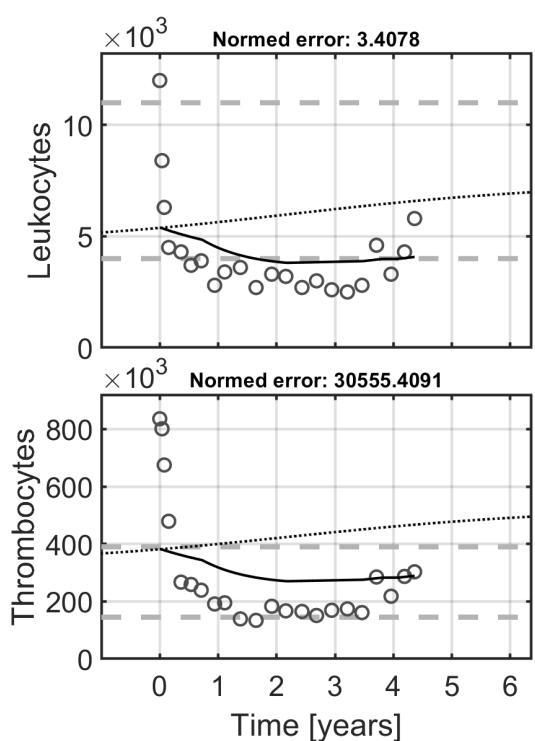
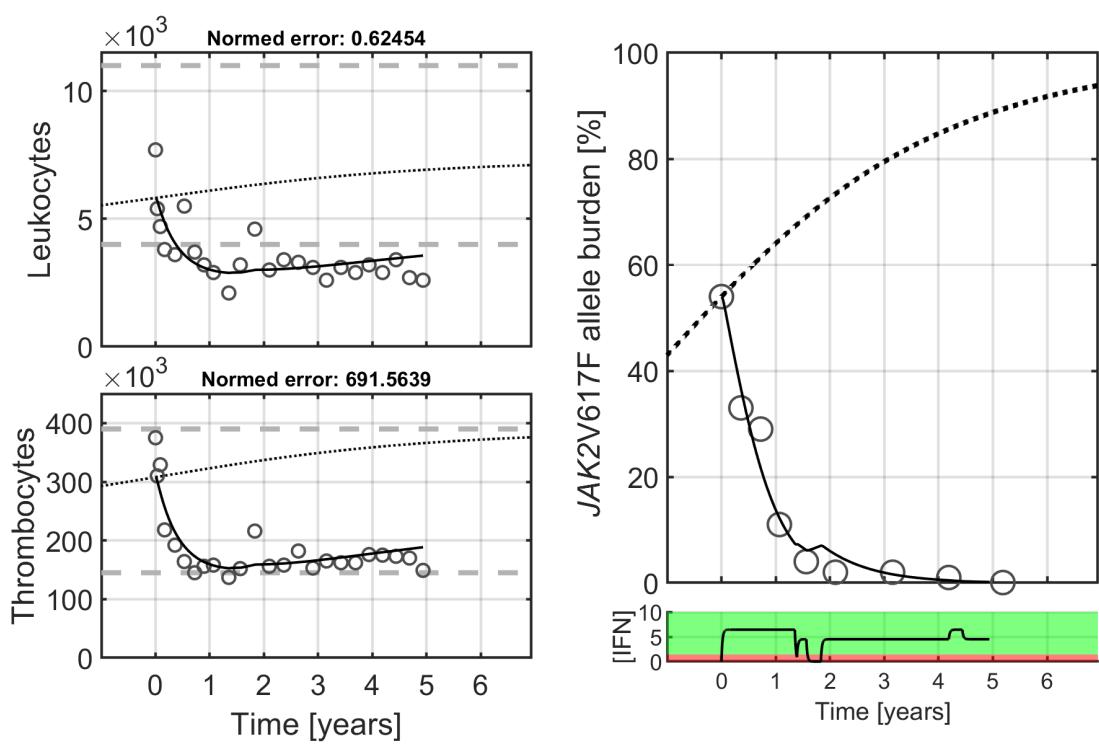
The right-hand panels displays the full model fit to all data, see the description in supplementary material B. The two left-hand panels display the sum of mature cells in the corresponding model simulation, scaled to fit with either the leukocytes or the thrombocyte. The resulting scaling-factor hence describes the assumed fraction of mature cells that correspond to the given cell-type. In the figures, the approximate healthy intervals are also shown, defined as between  $4 \cdot 10^3$  to  $11 \cdot 10^3$  per microliter of blood for leukocytes and  $145 \cdot 10^3$  to  $390 \cdot 10^3$  per microliter of blood thrombocytes. We emphasize that the patient-specific response to IFN in the model was only fit to the data for the *JAK2V617F* allele burden, and the scaling of the mature cell counts was done subsequently, independent of the IFN blood-concentration.

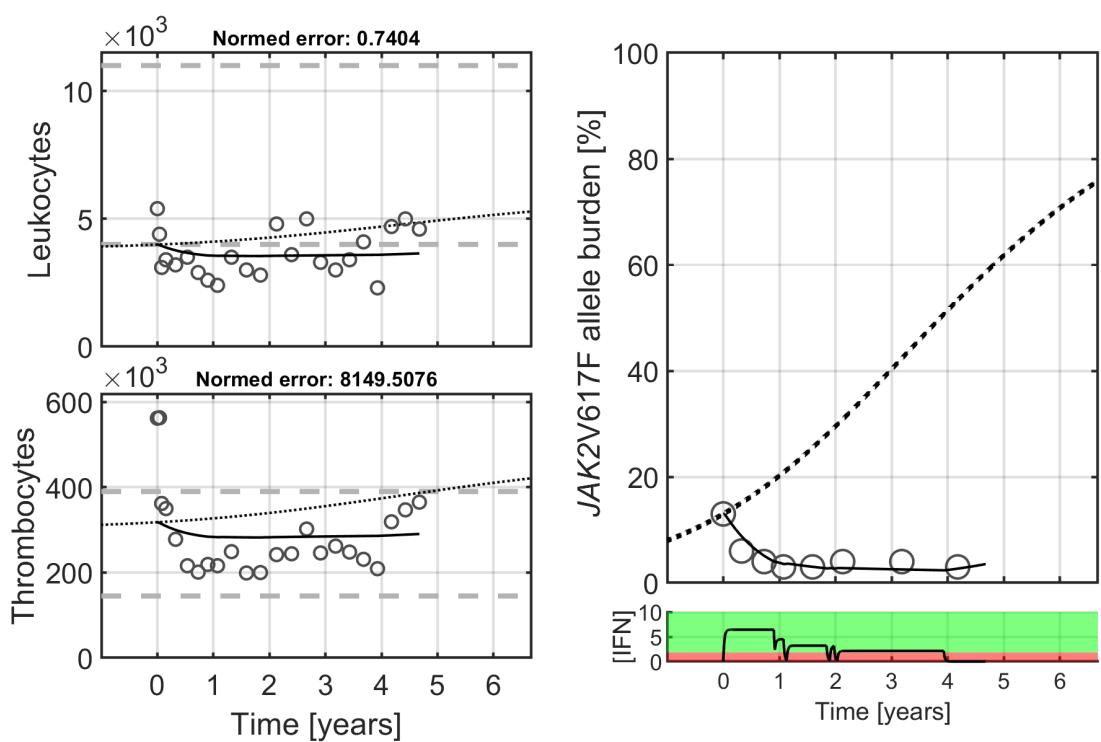
At the top of the leukocytes and thrombocyte figures, a goodness-of-fit-metric of the best fit is shown, defined as the sum of squared errors, divided by the number of points used in the fit. A low number signifies a good fit. Note that the error metric depends on the order of magnitude of the data, and hence the metric is typically higher for thrombocytes than for leukocytes.

**Patient P002**

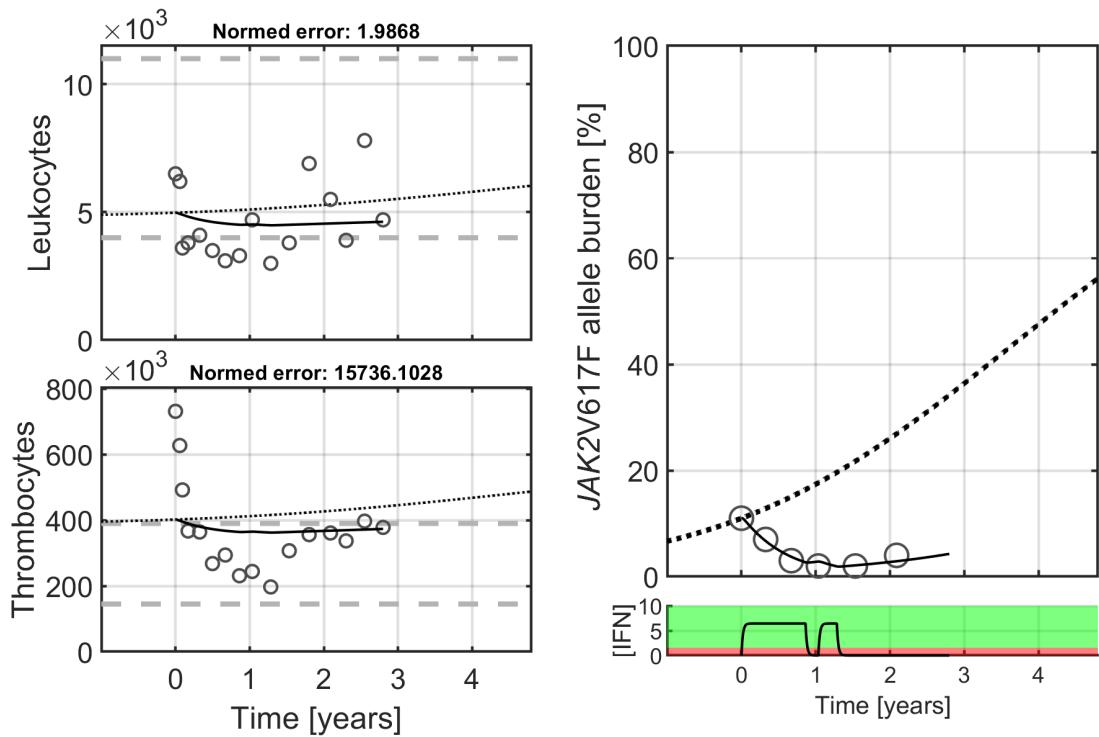


**Patient P003**

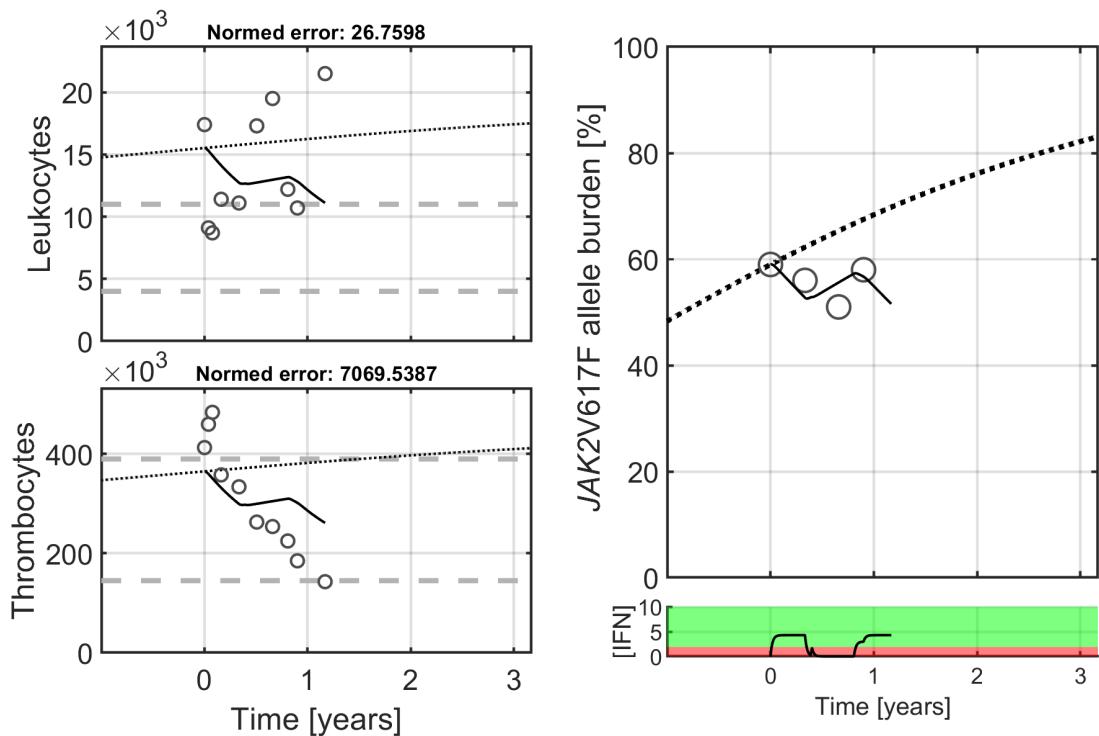




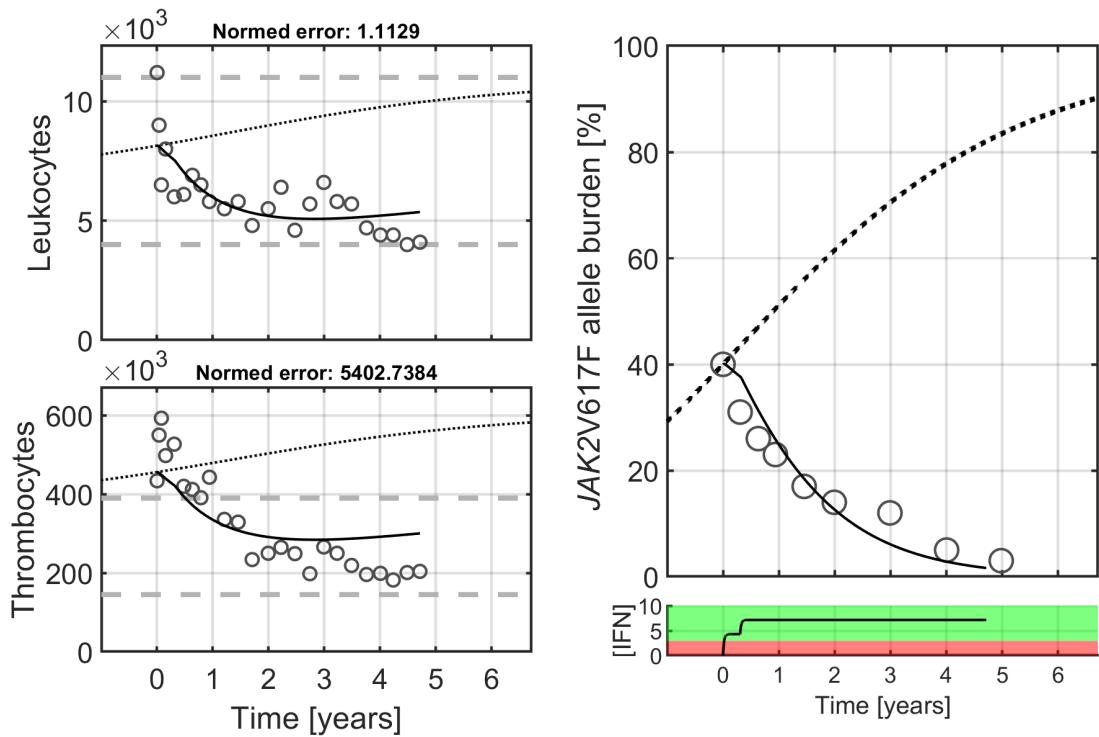
Patient P011



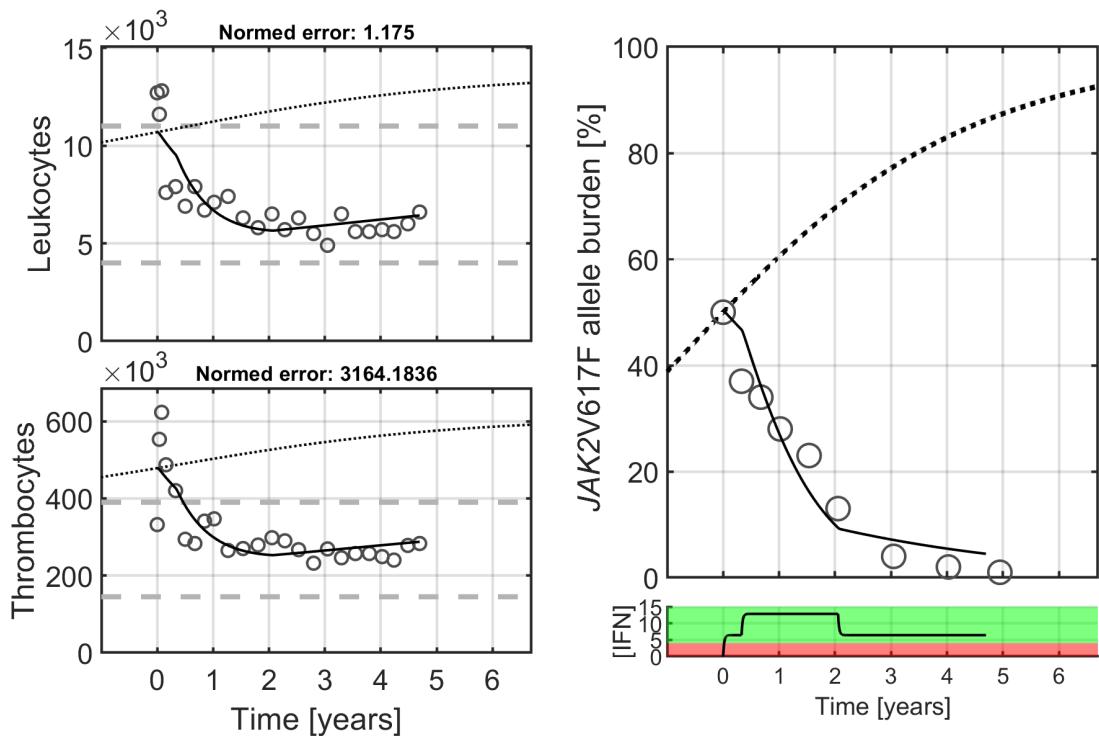
Patient P014



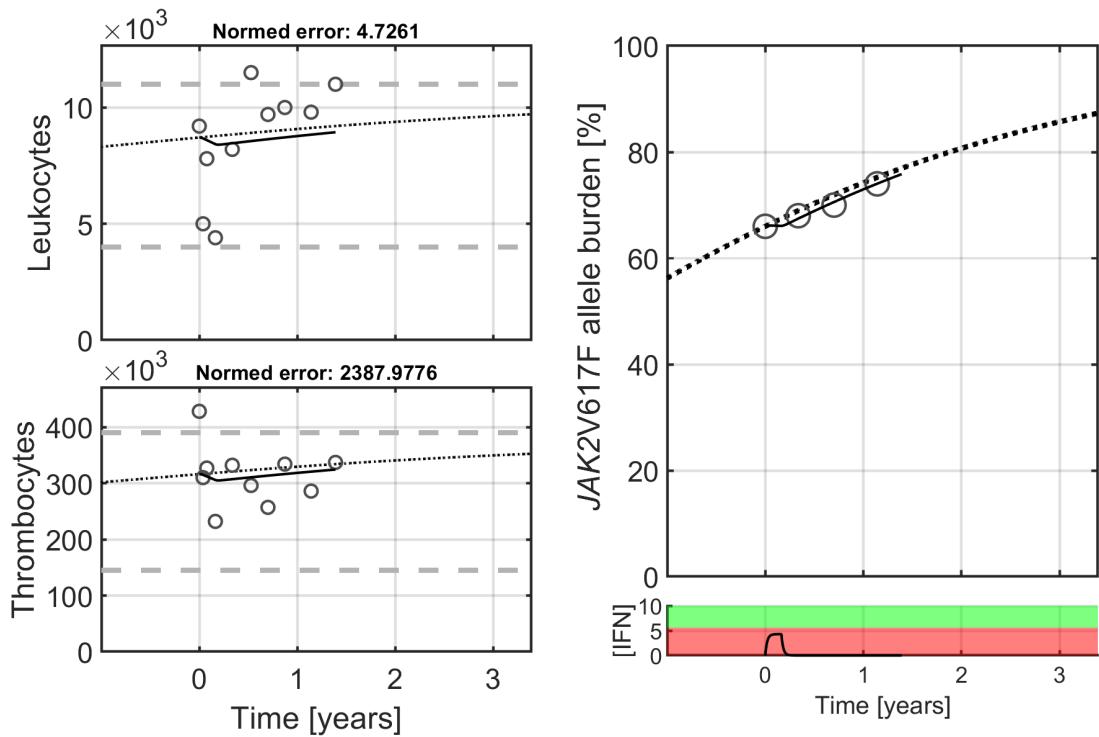
Patient P016



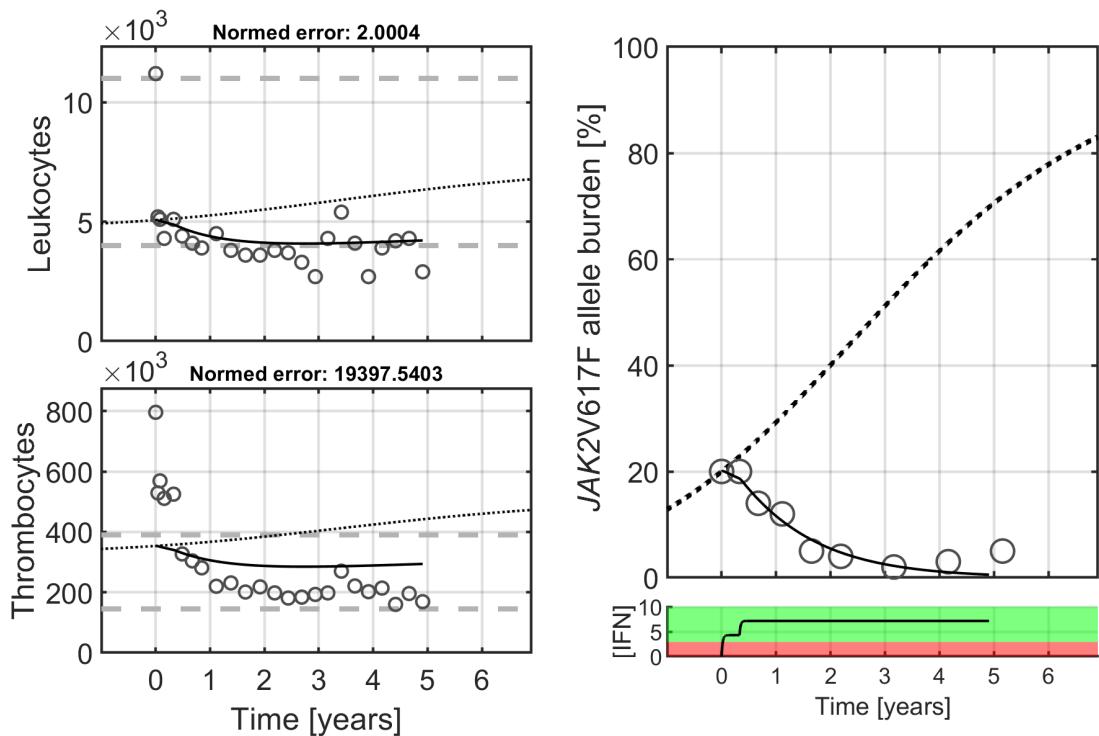
Patient P021



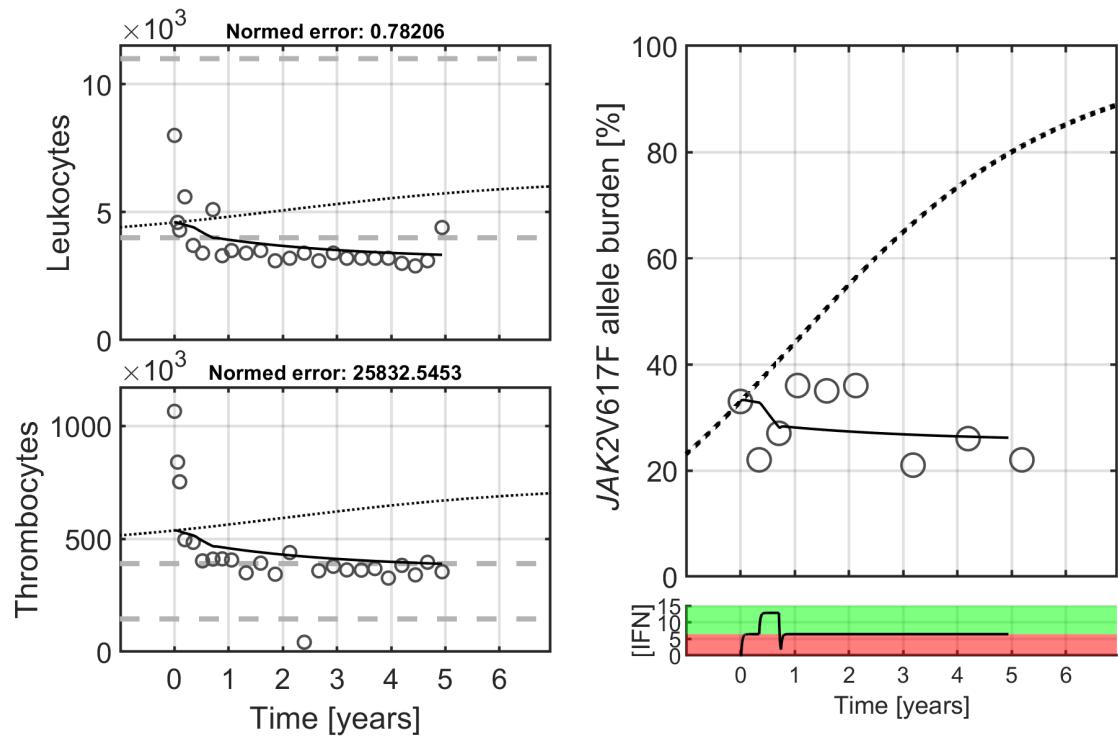
Patient P026



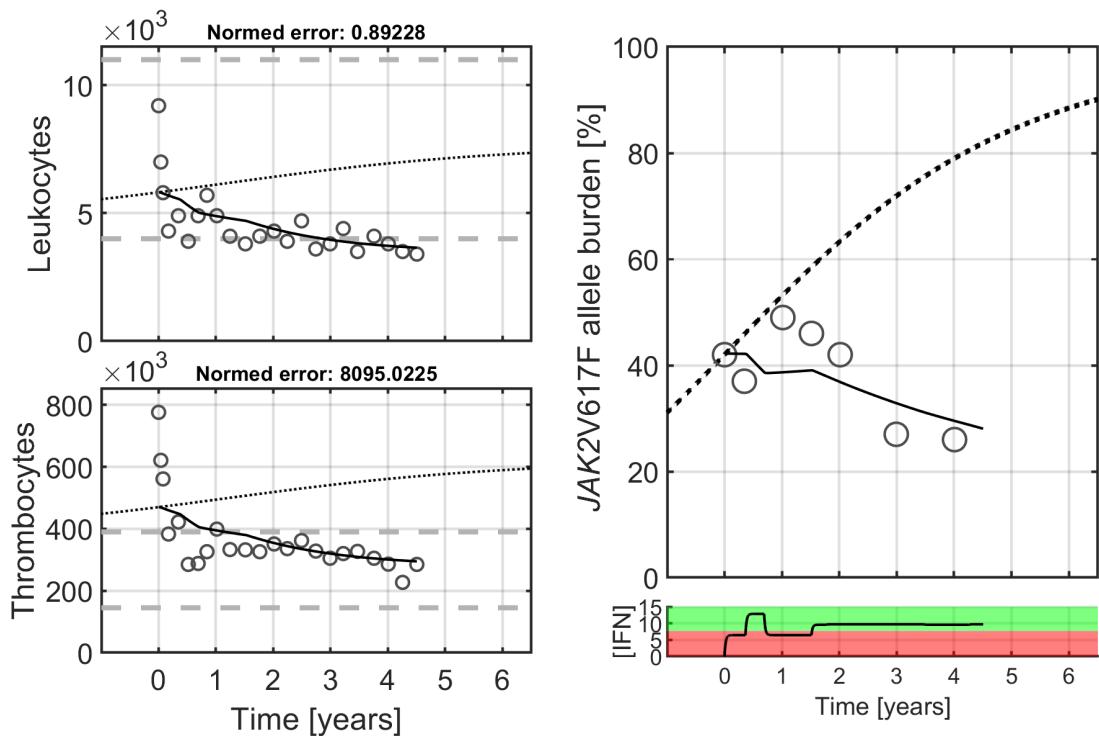
Patient P028



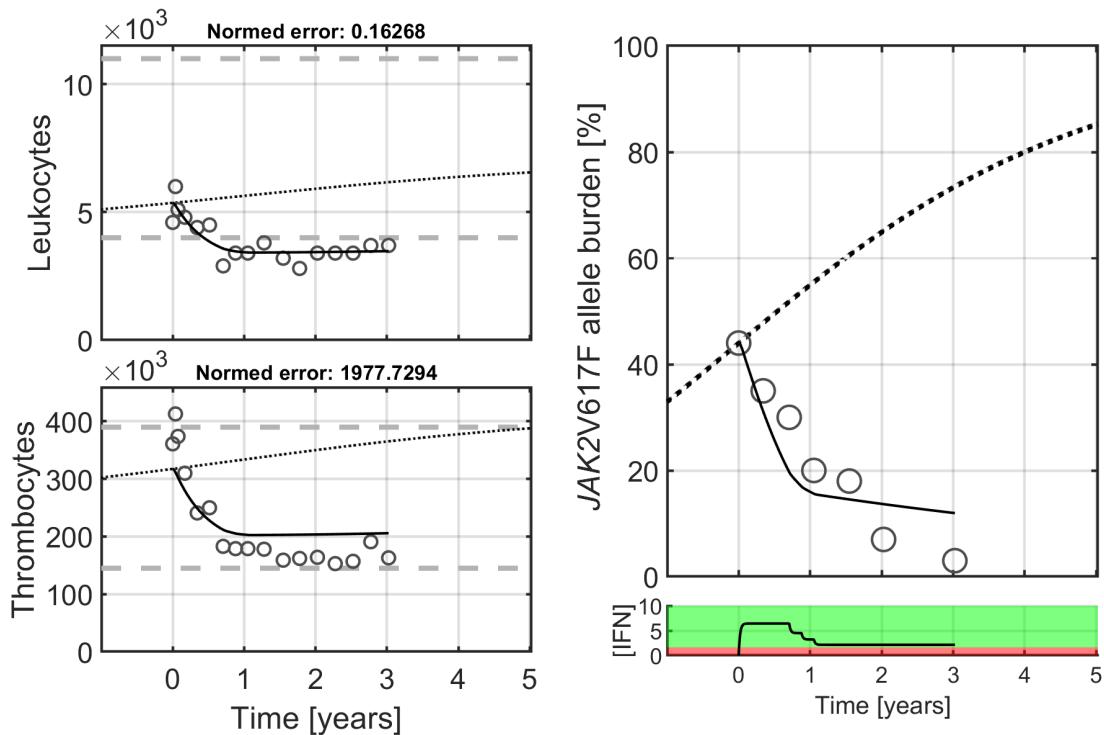
Patient P035



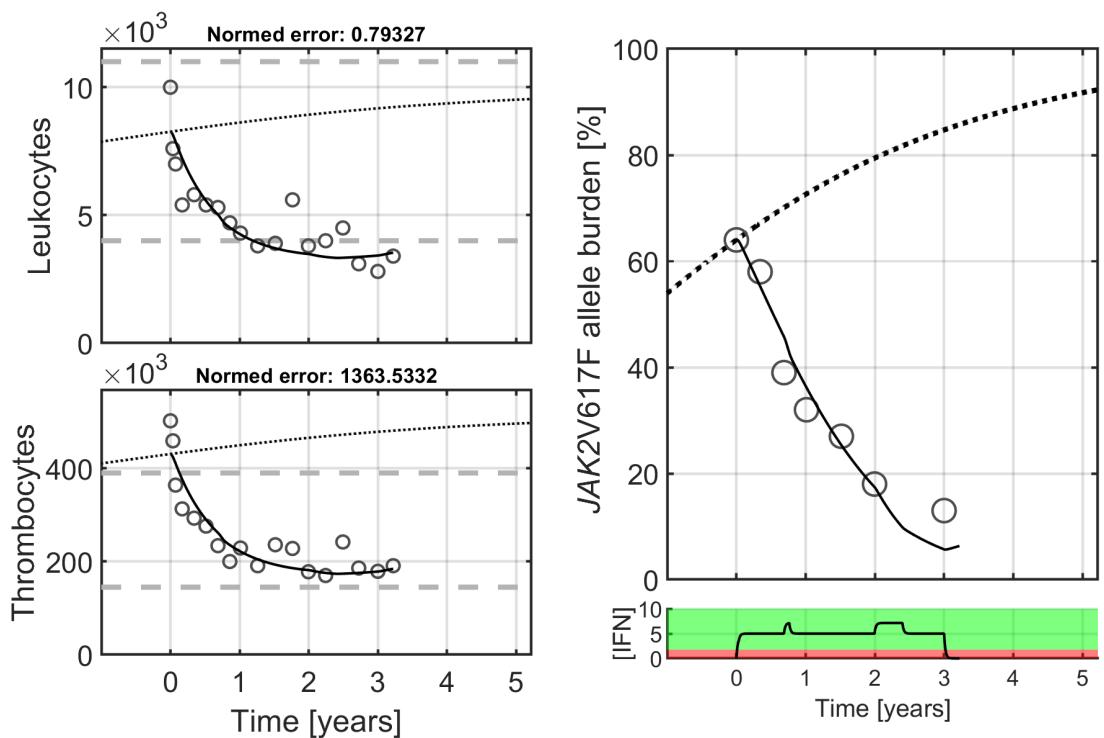
Patient P039



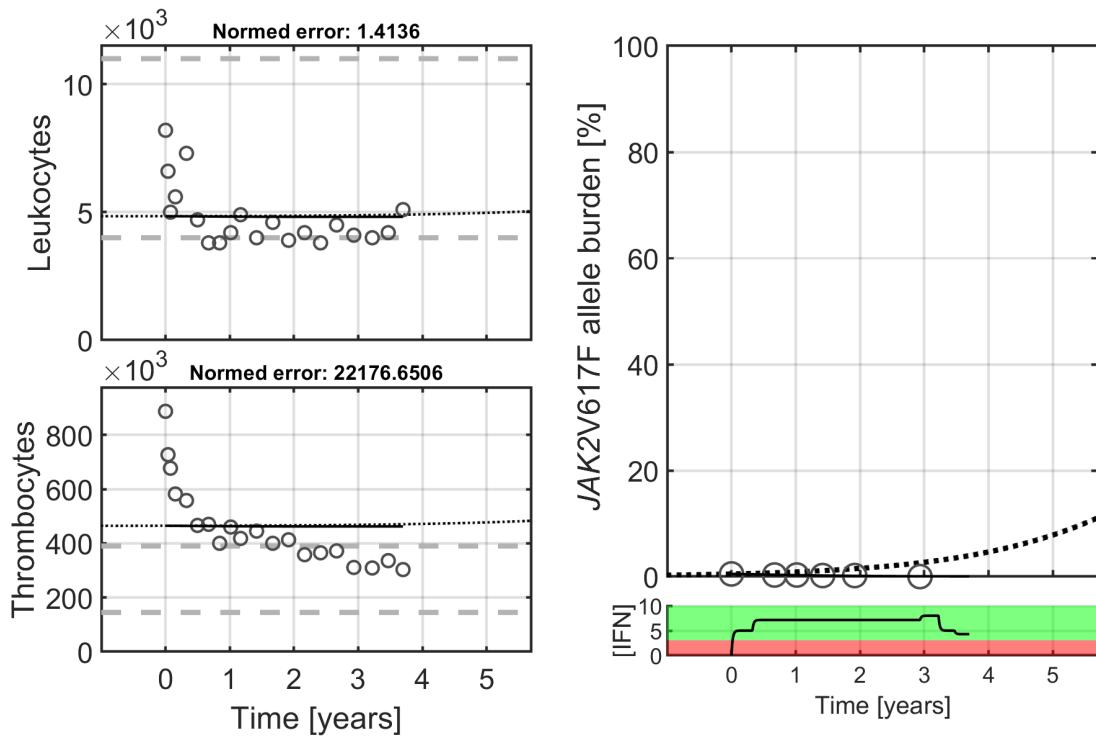
### Patient P045



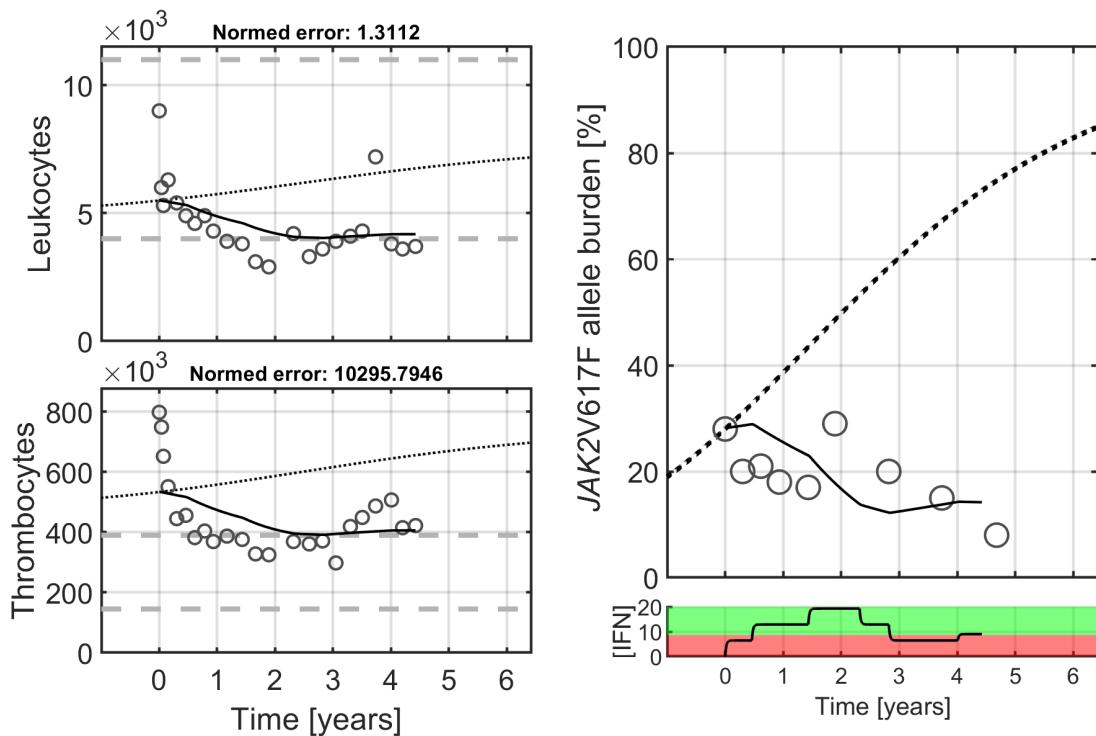
### Patient P046



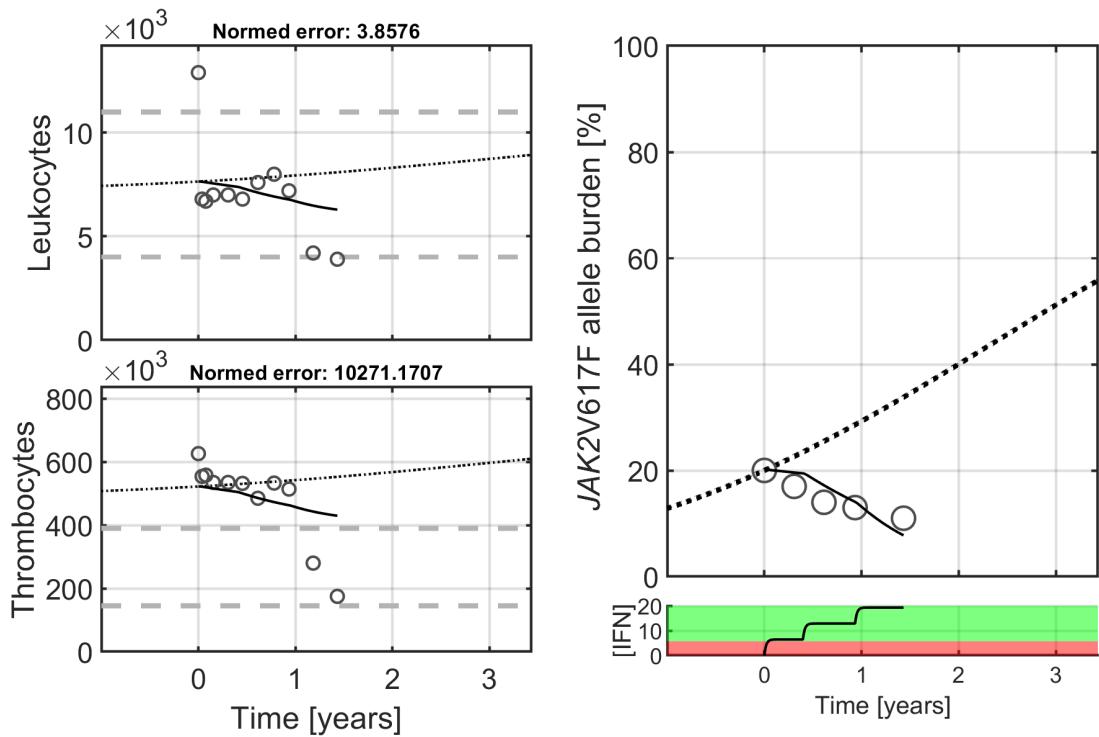
### Patient P049



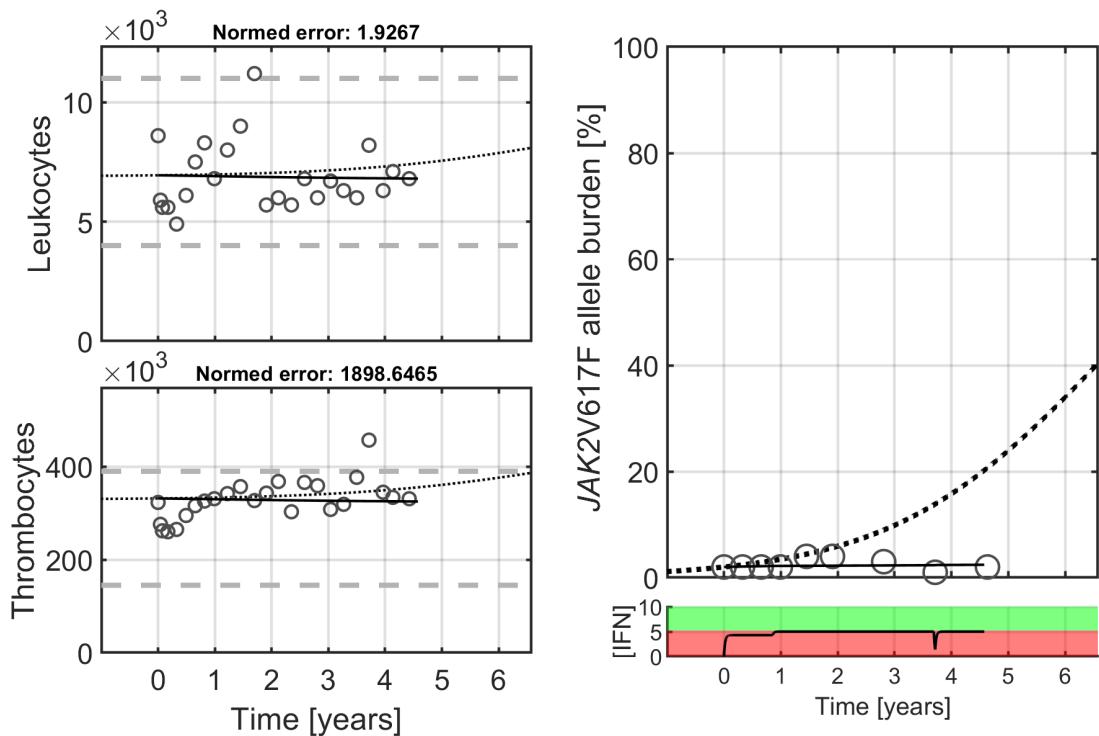
### Patient P062



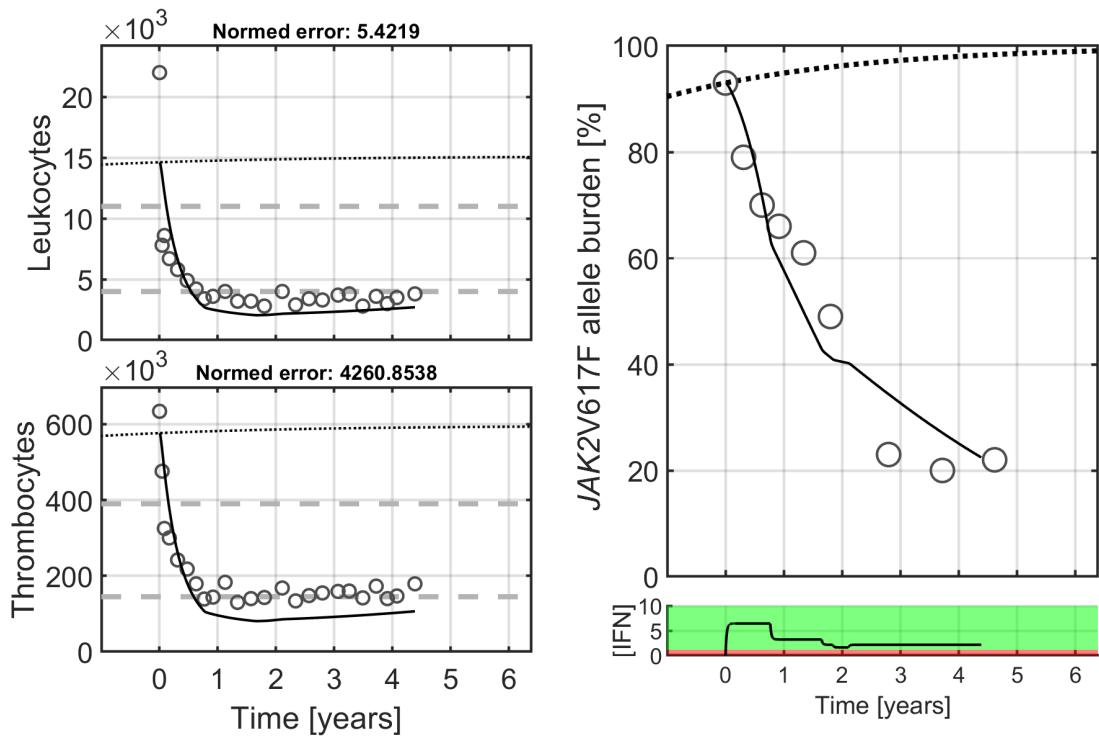
Patient P067



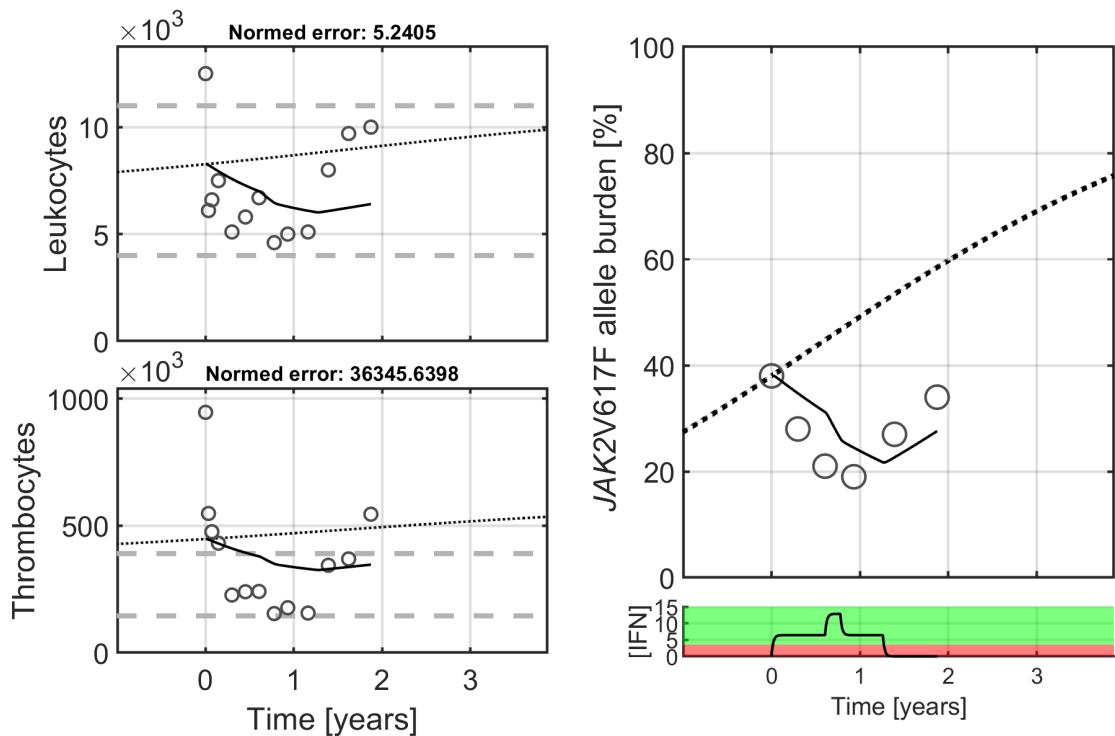
Patient P070



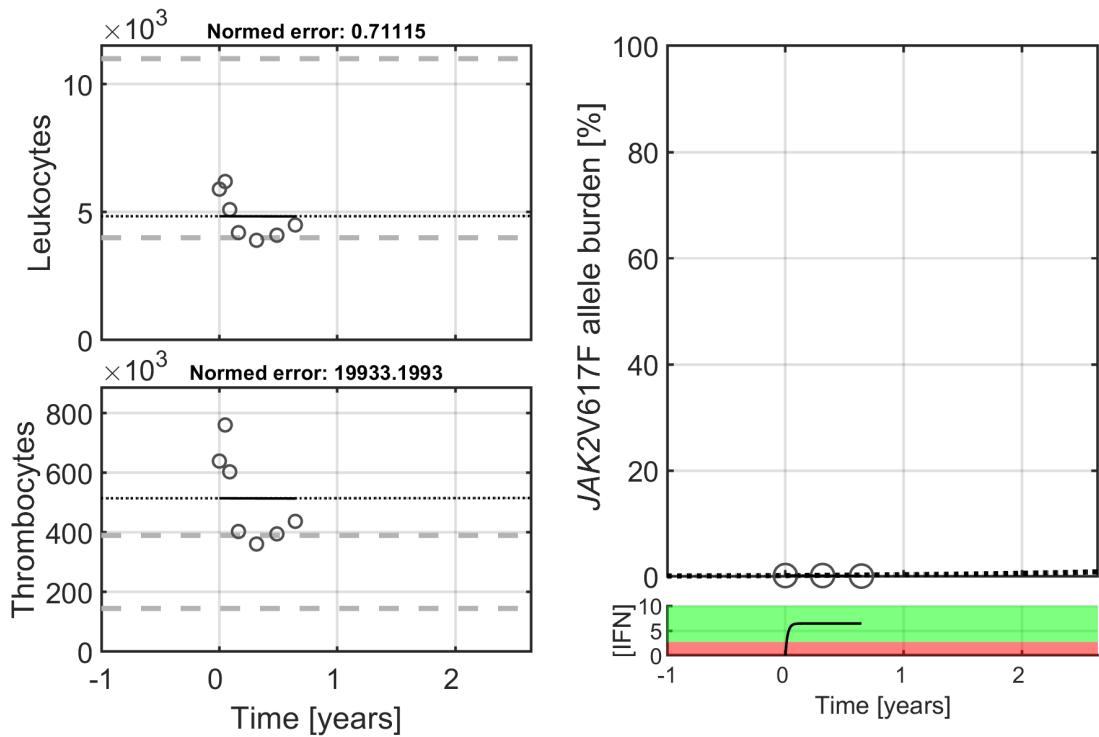
Patient P075



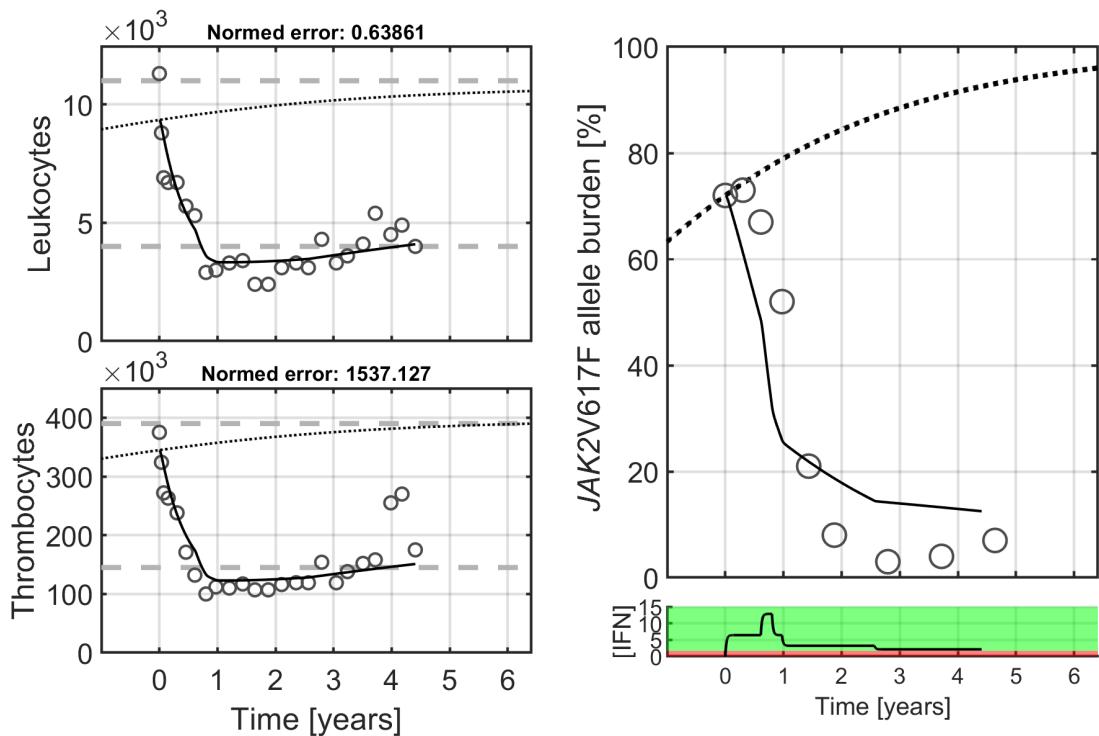
Patient P078



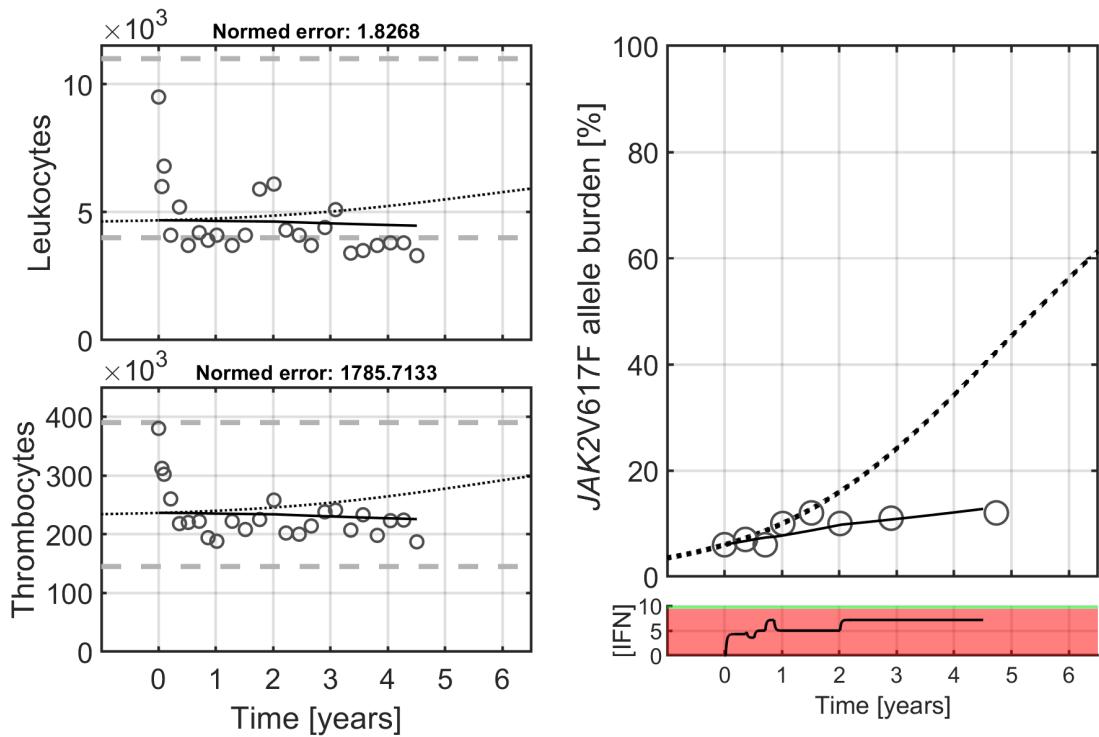
Patient P079



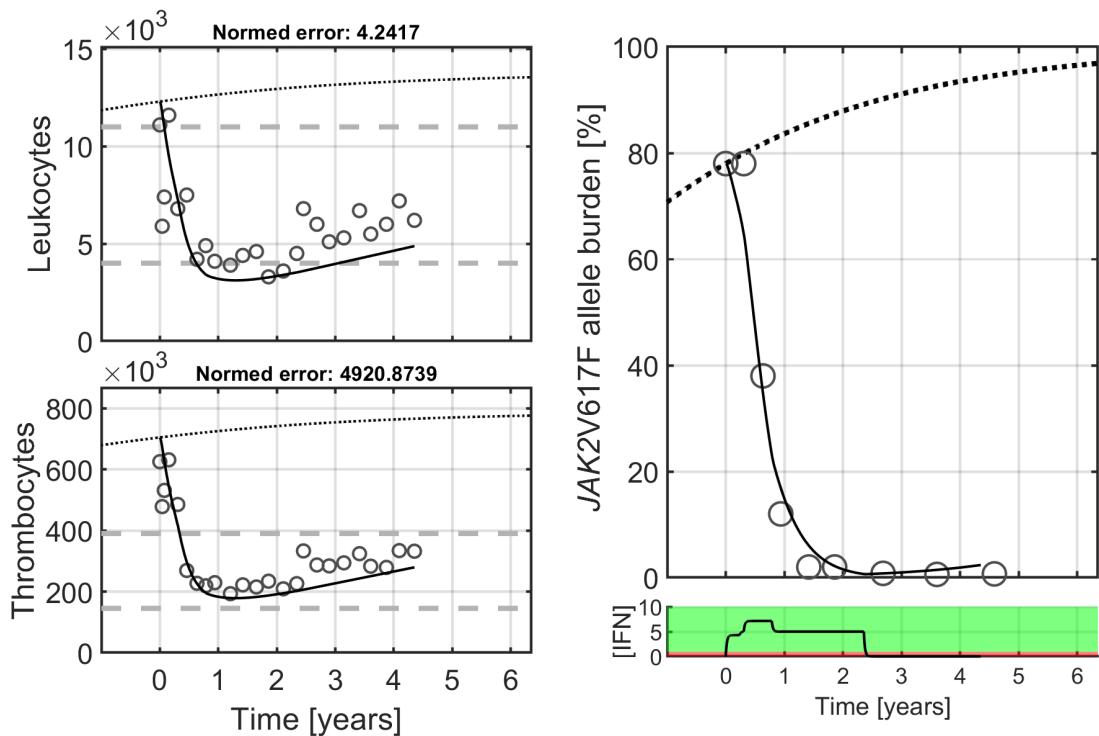
Patient P082



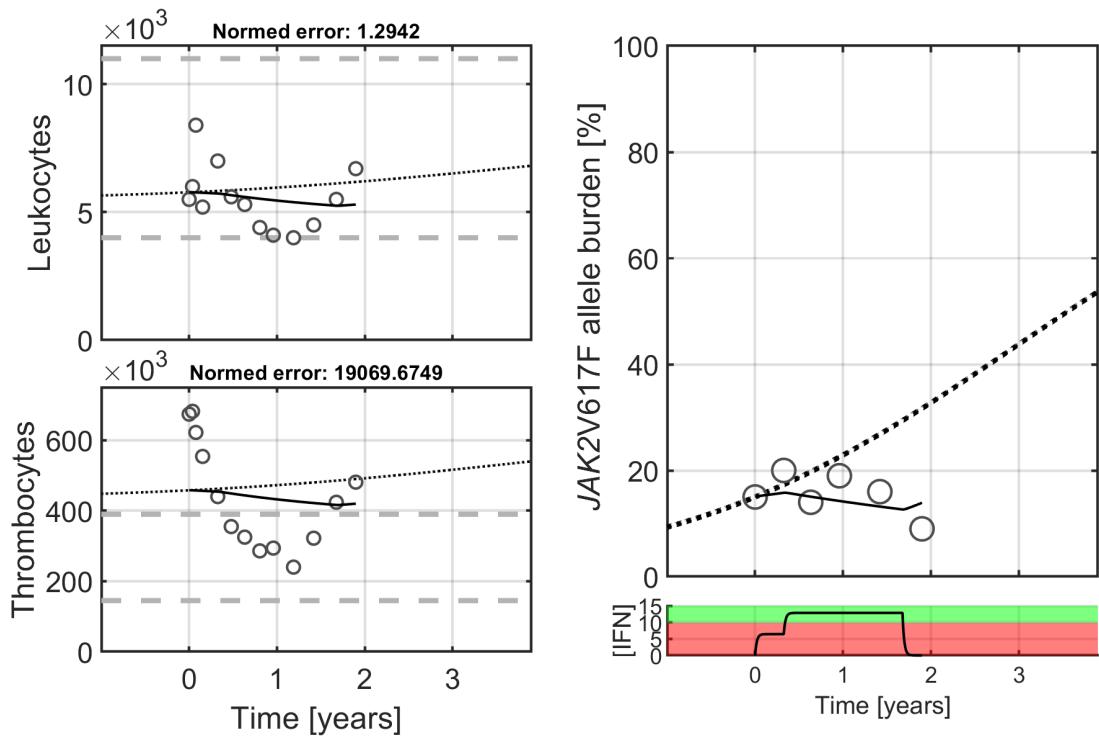
Patient P084



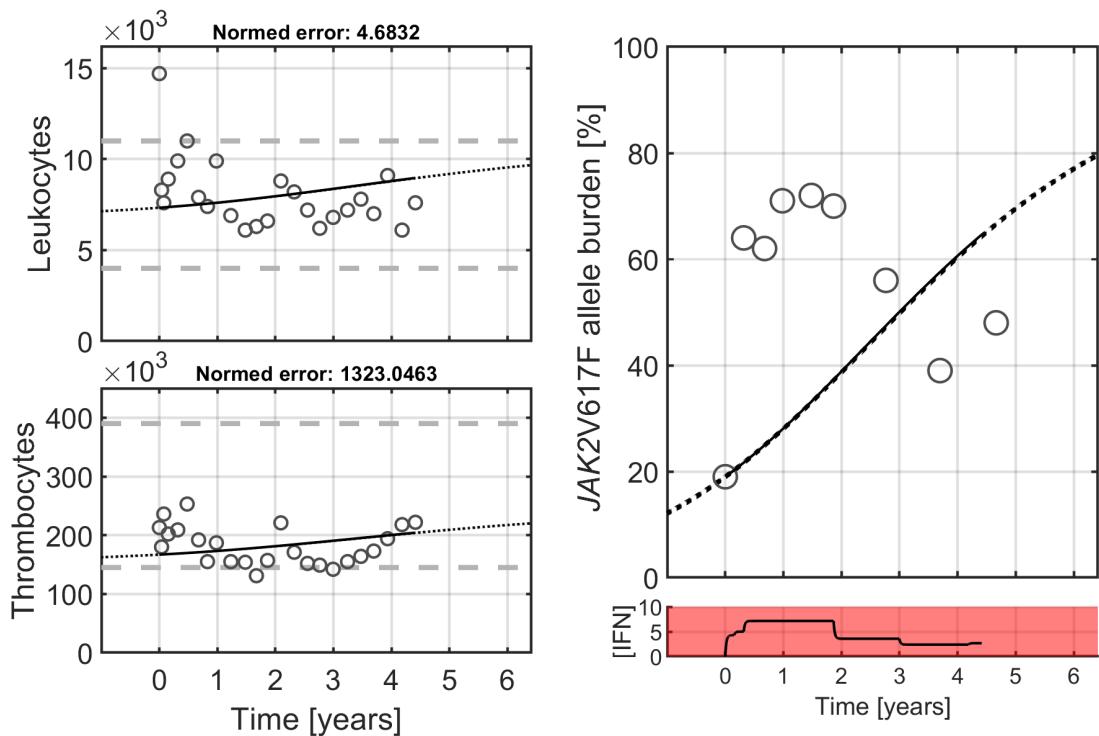
Patient P086



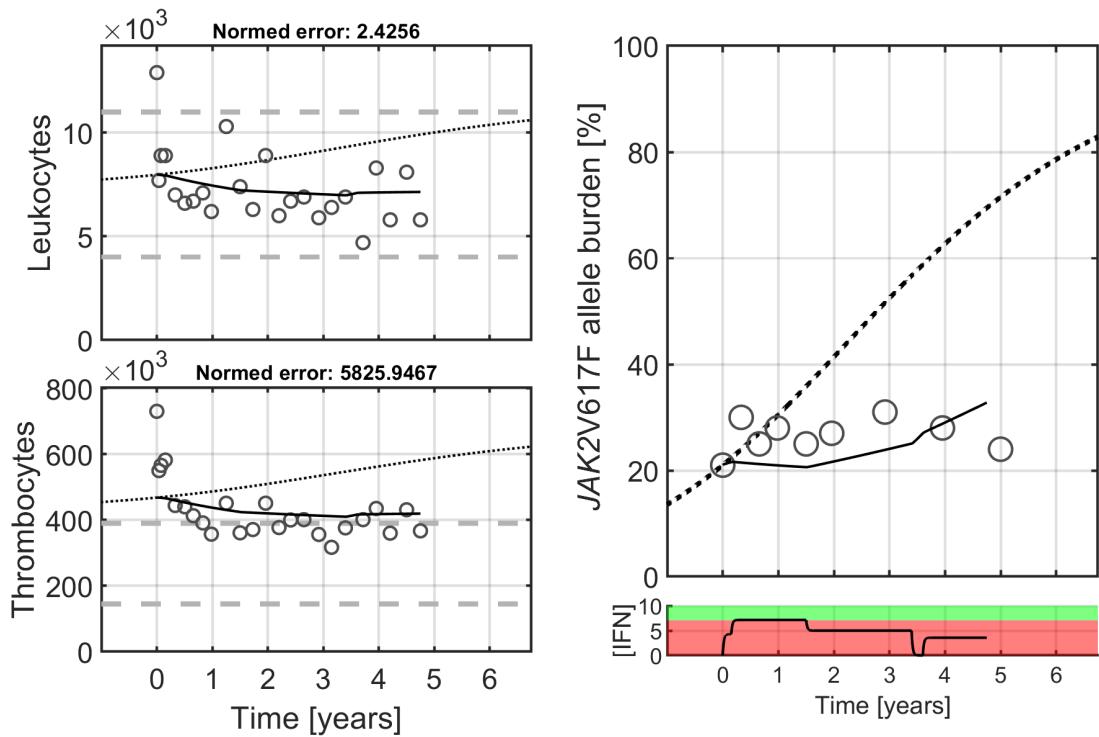
Patient P087



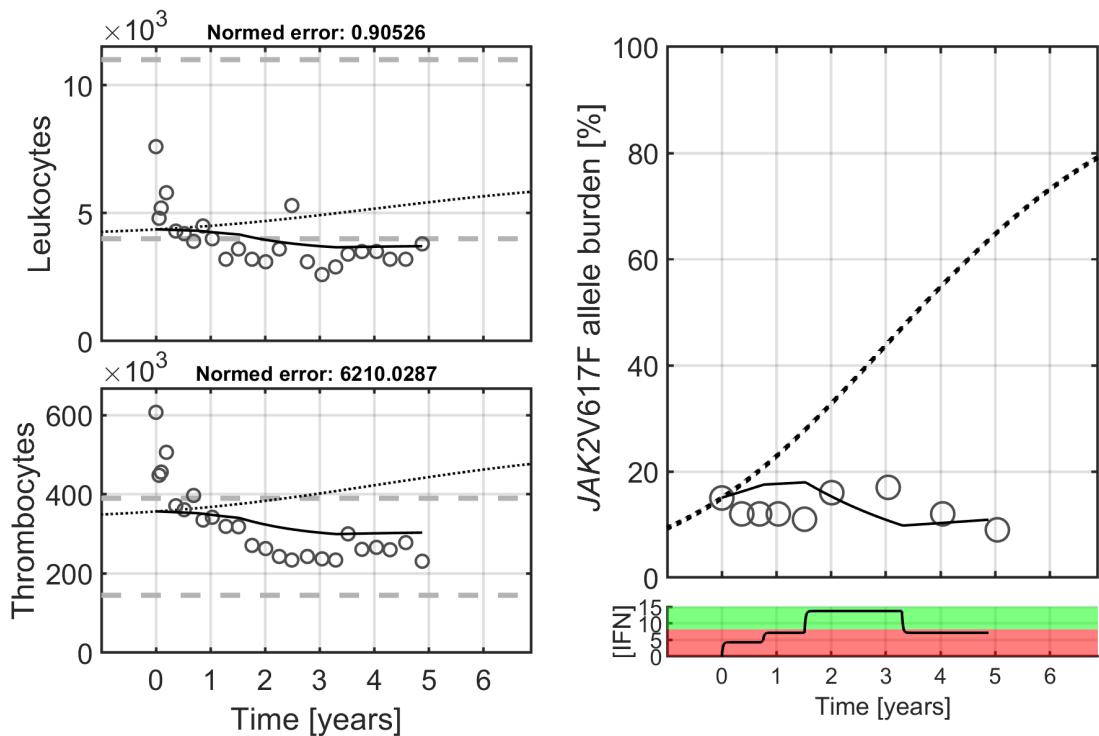
Patient P089



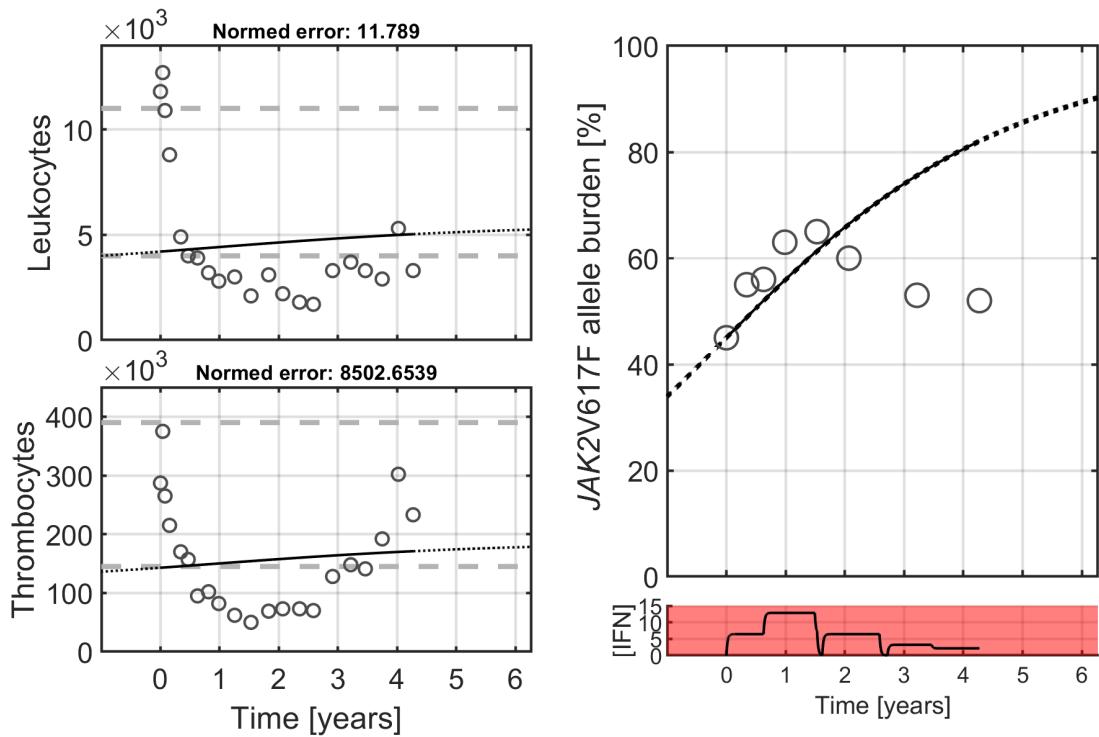
Patient P105



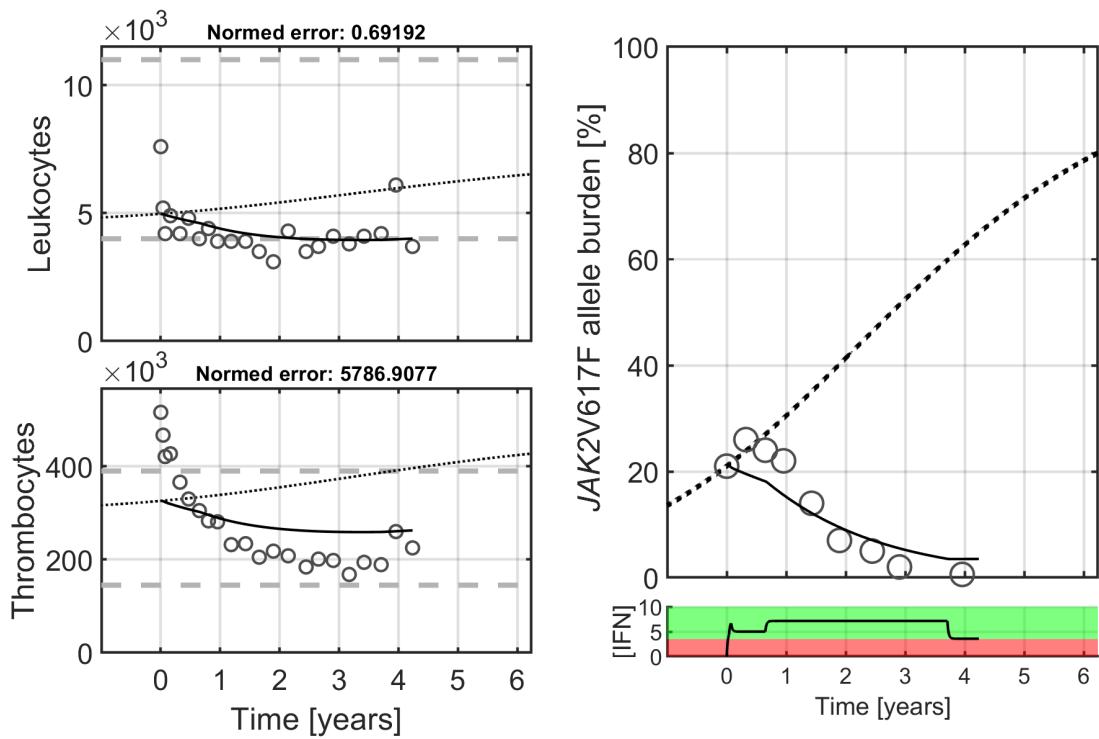
Patient P106



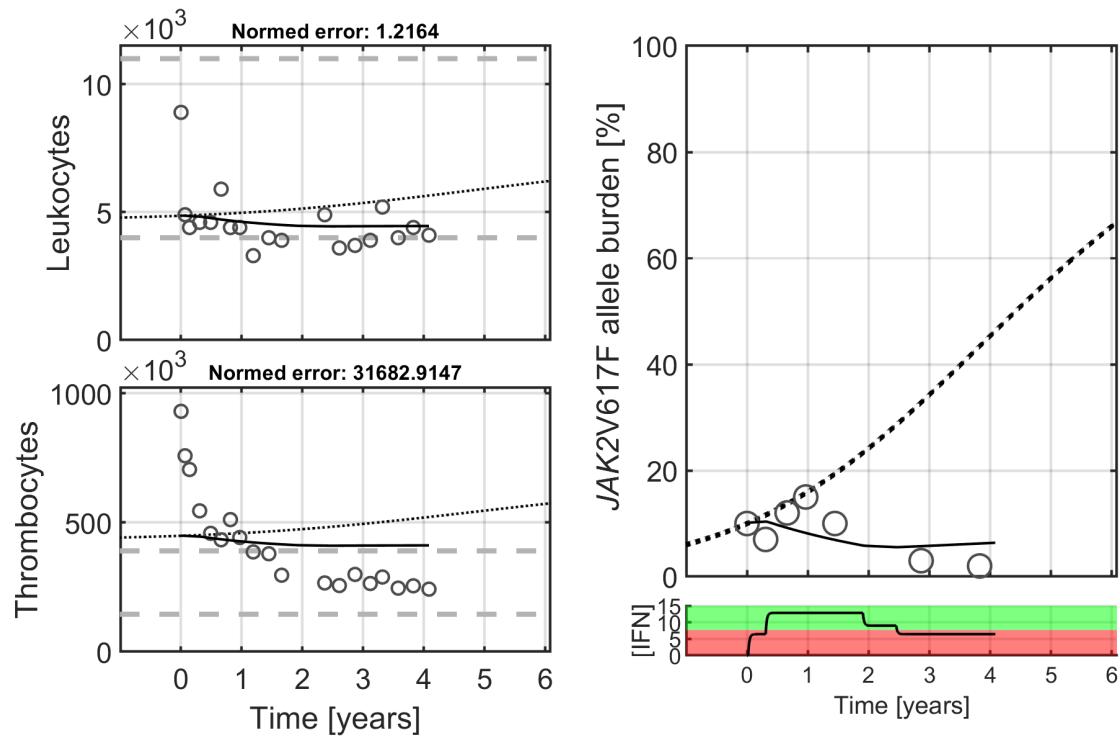
Patient P111



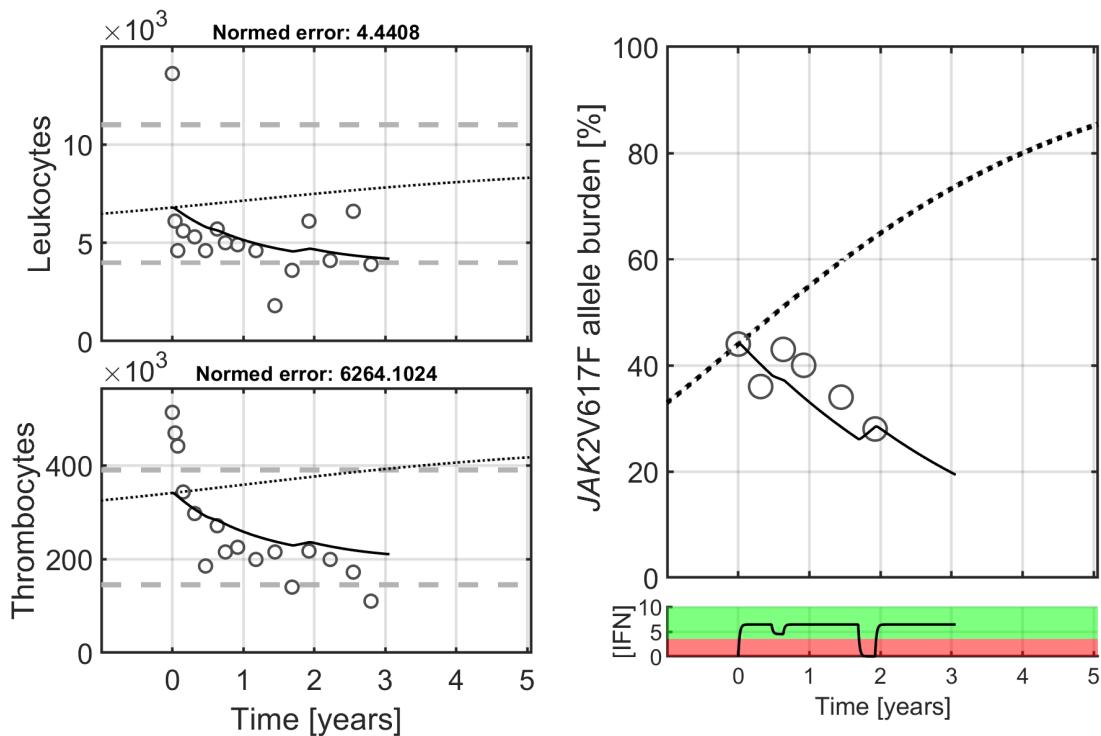
Patient P113



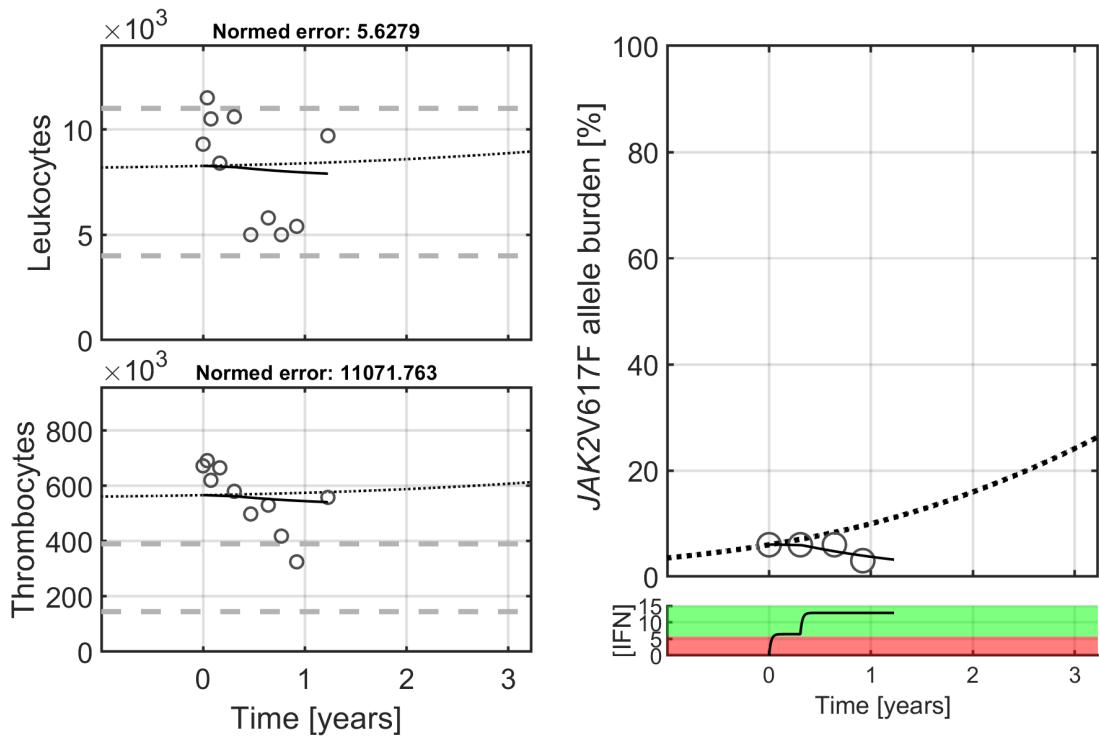
Patient P114



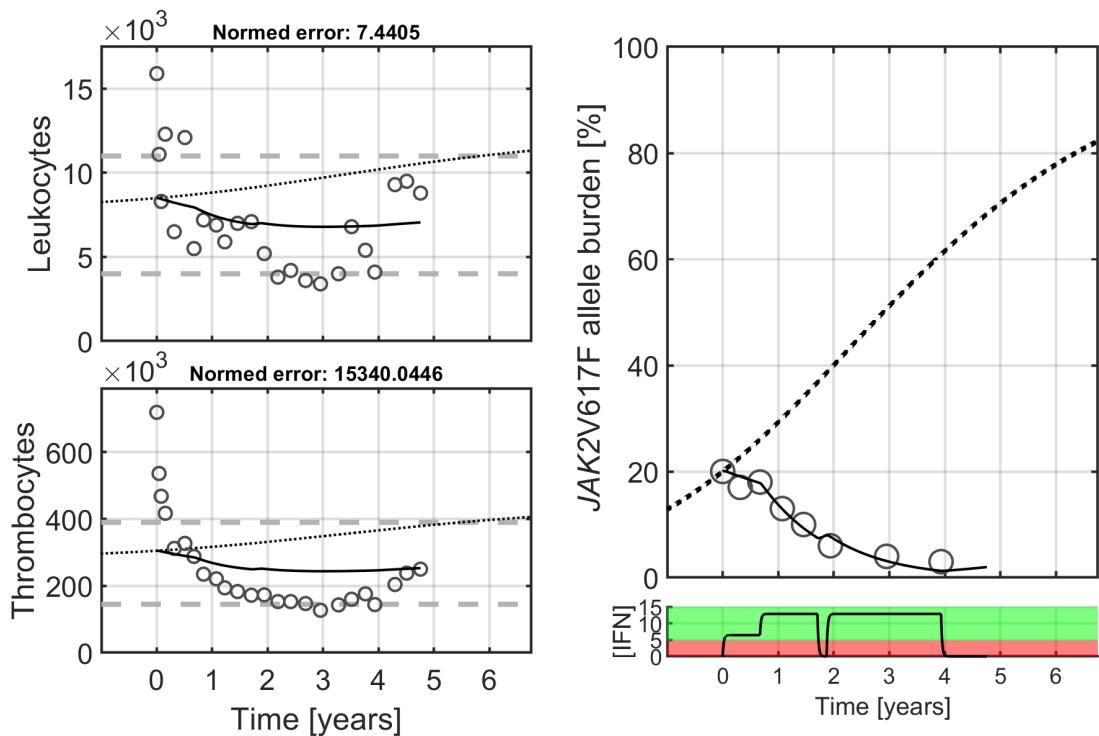
Patient P117



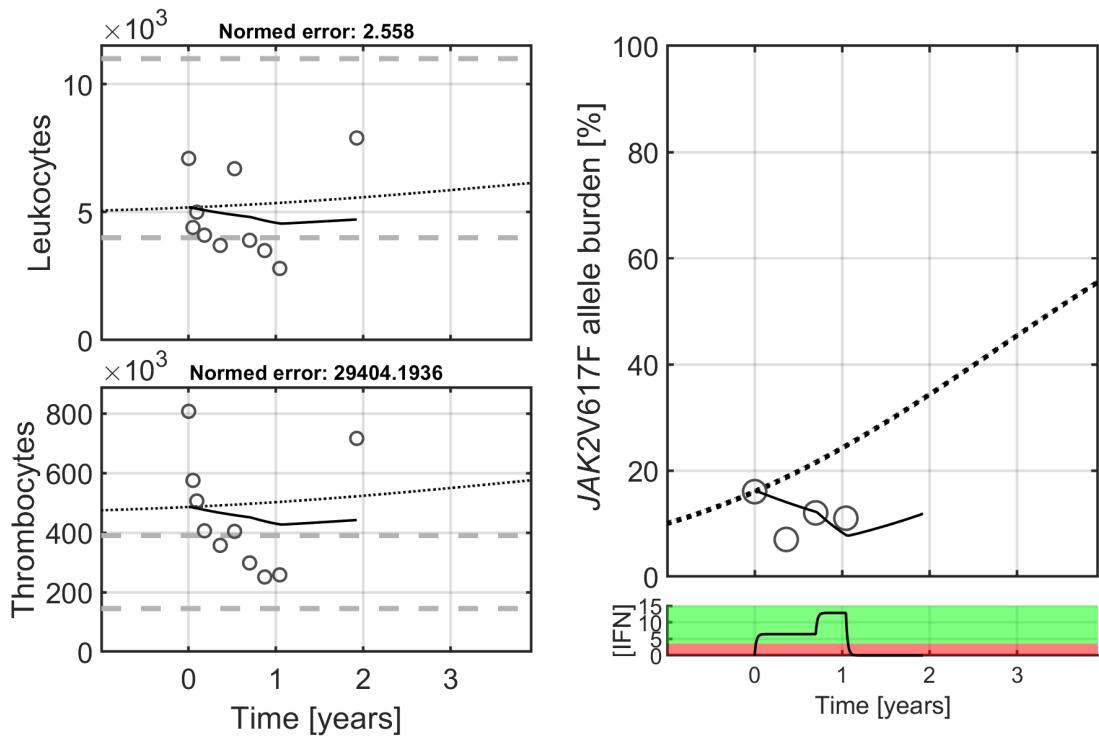
Patient P122



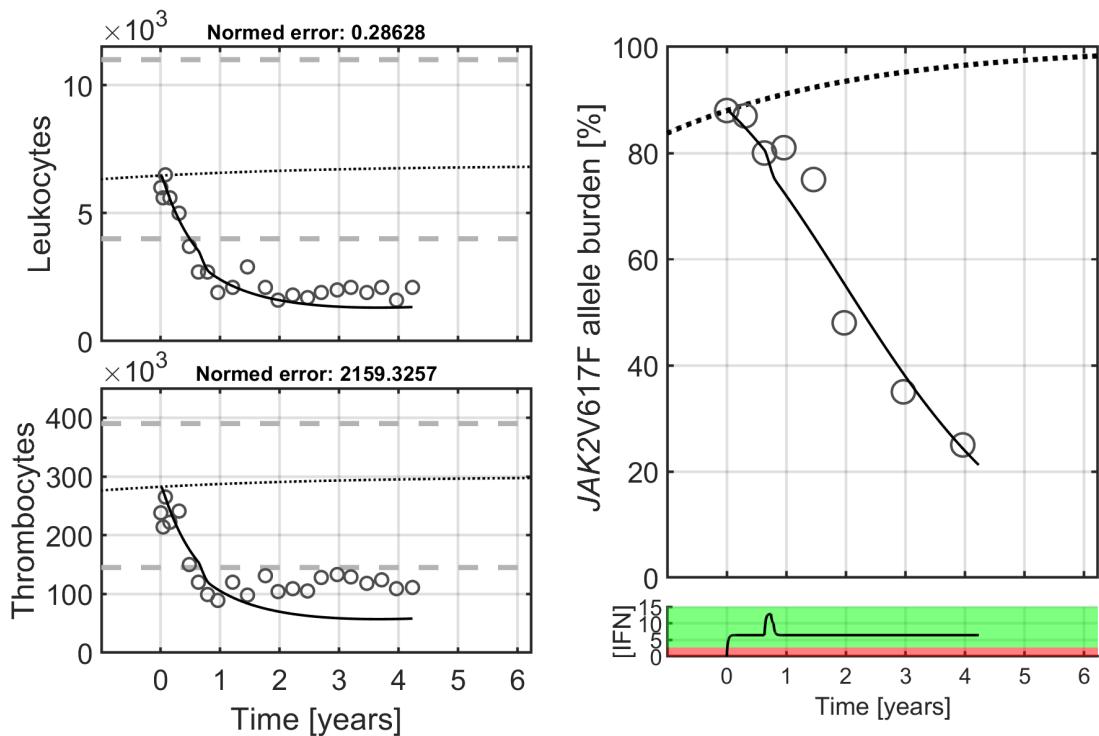
Patient P124



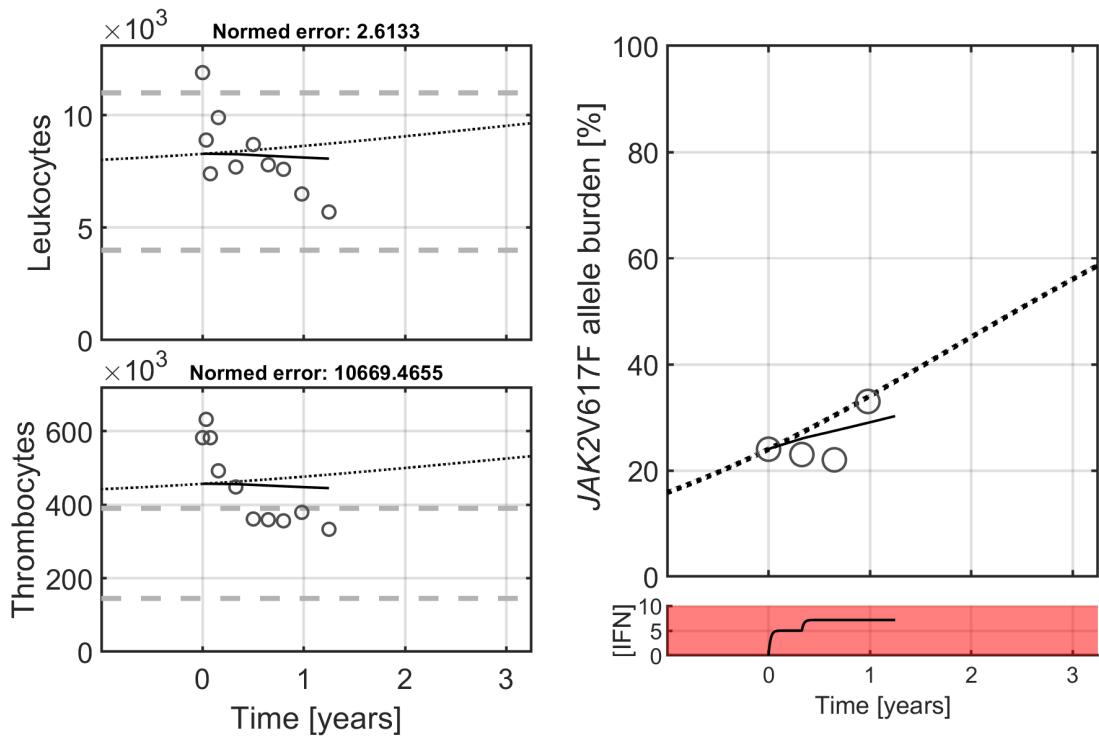
Patient P125



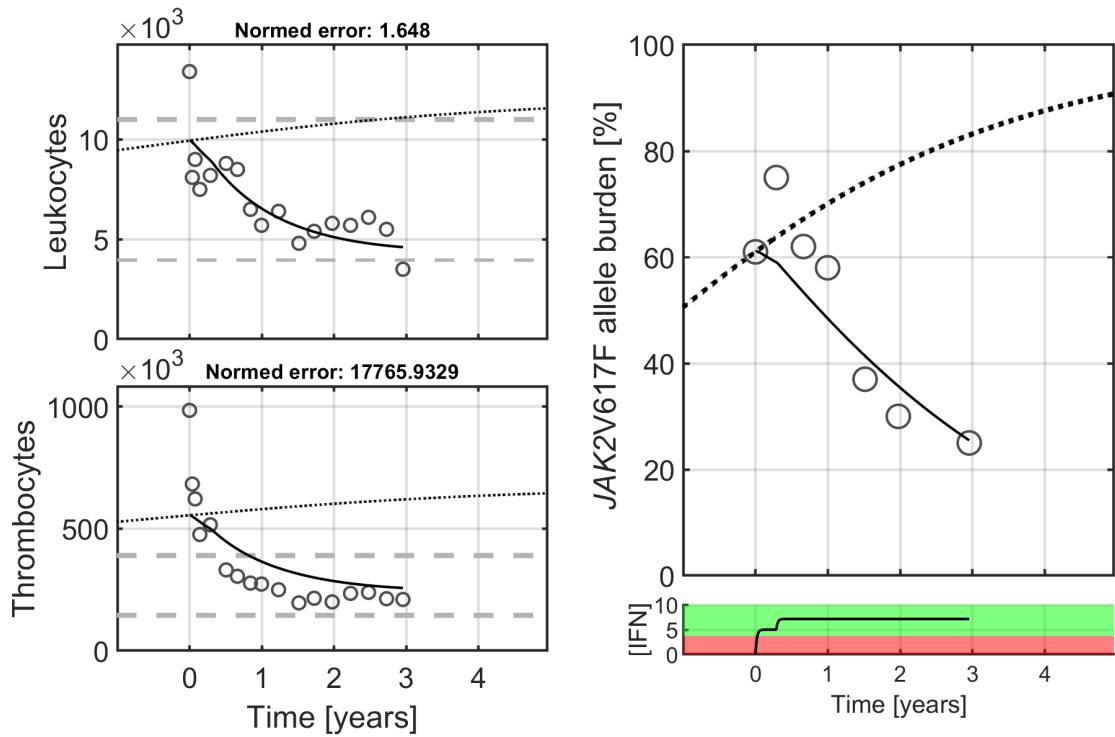
Patient P129



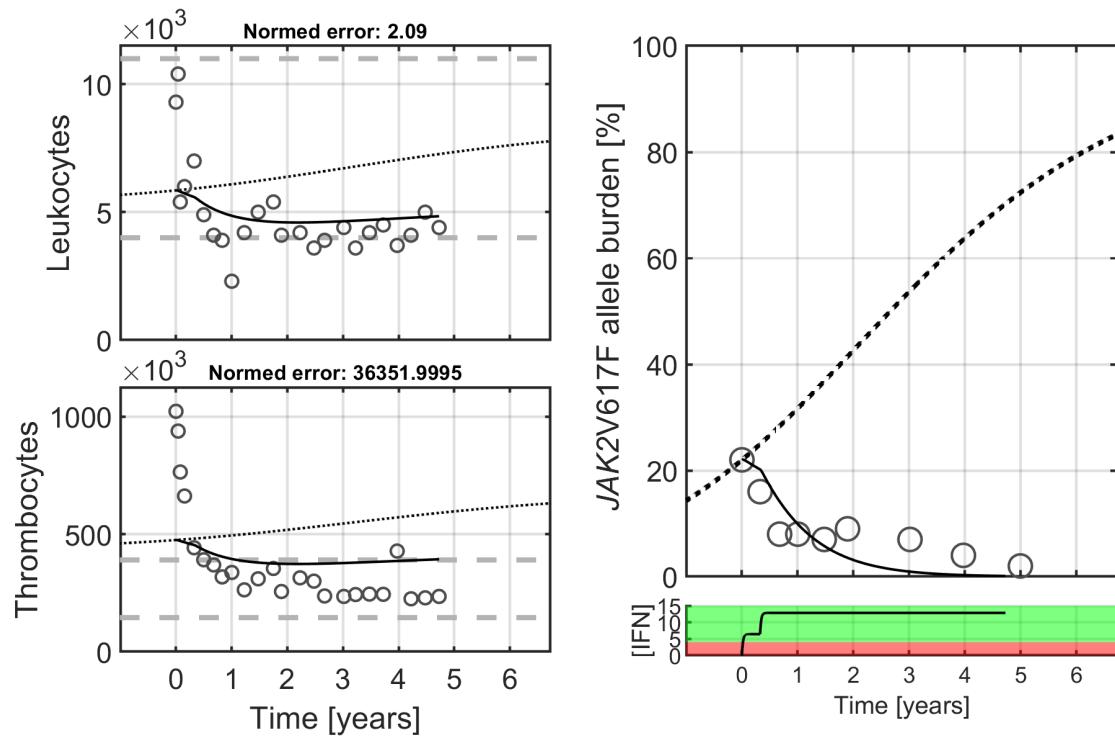
**Patient P131**



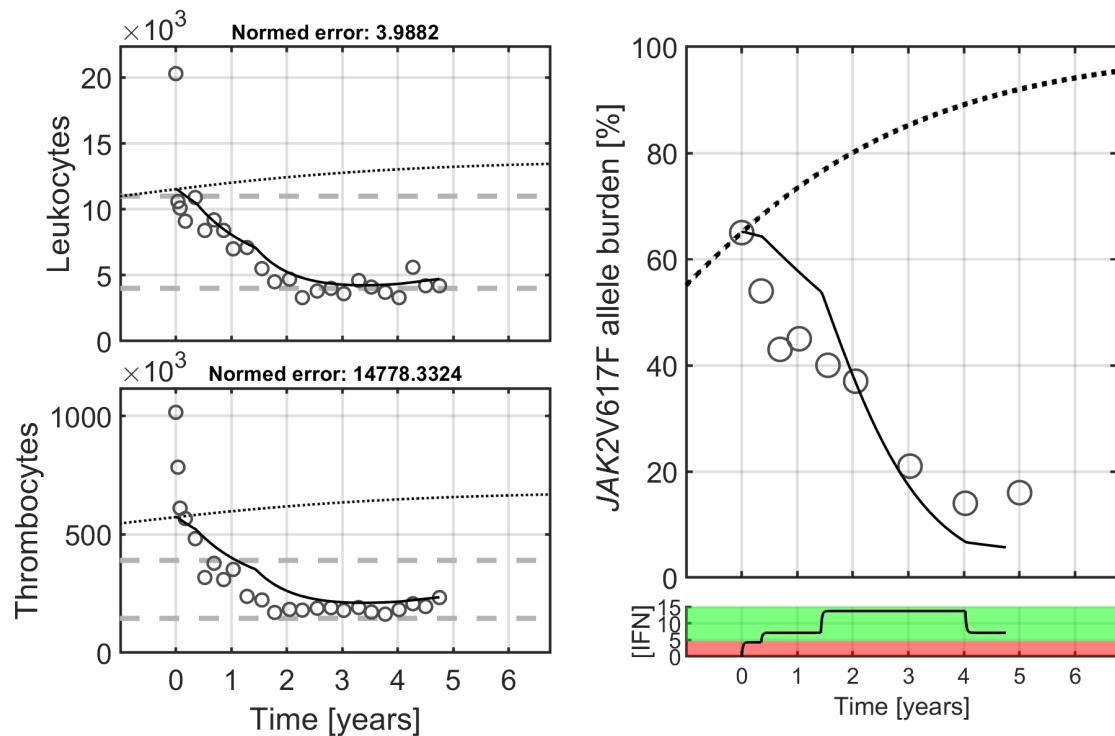
**Patient P135**



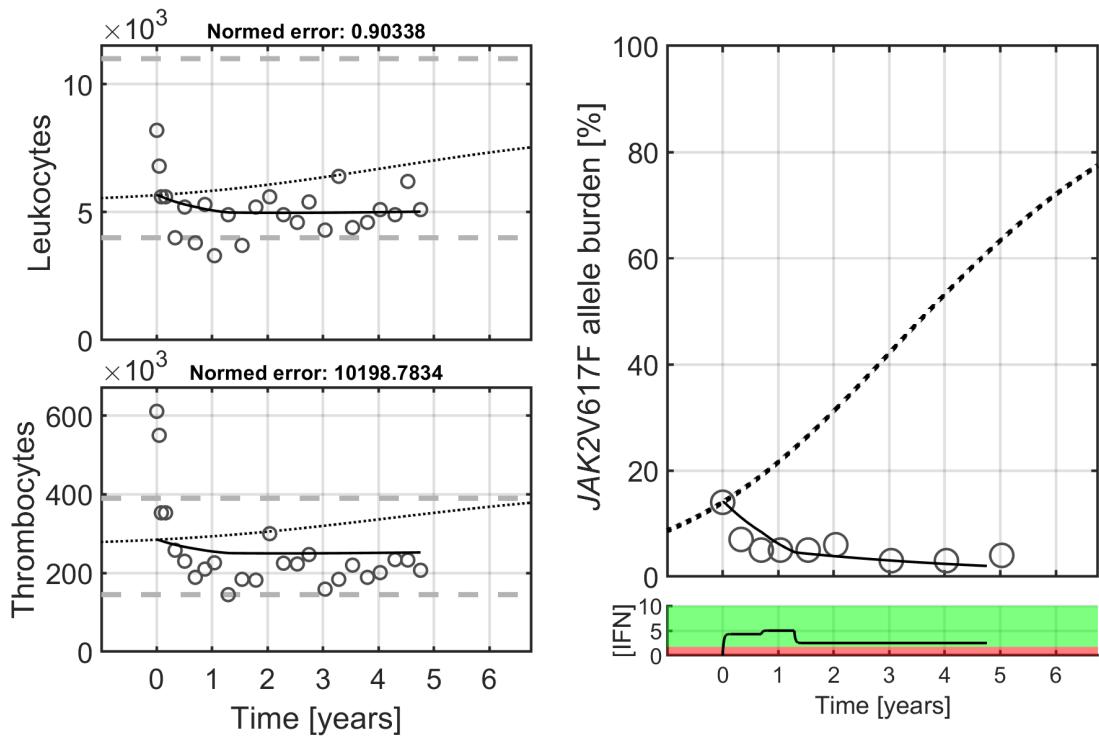
Patient P139



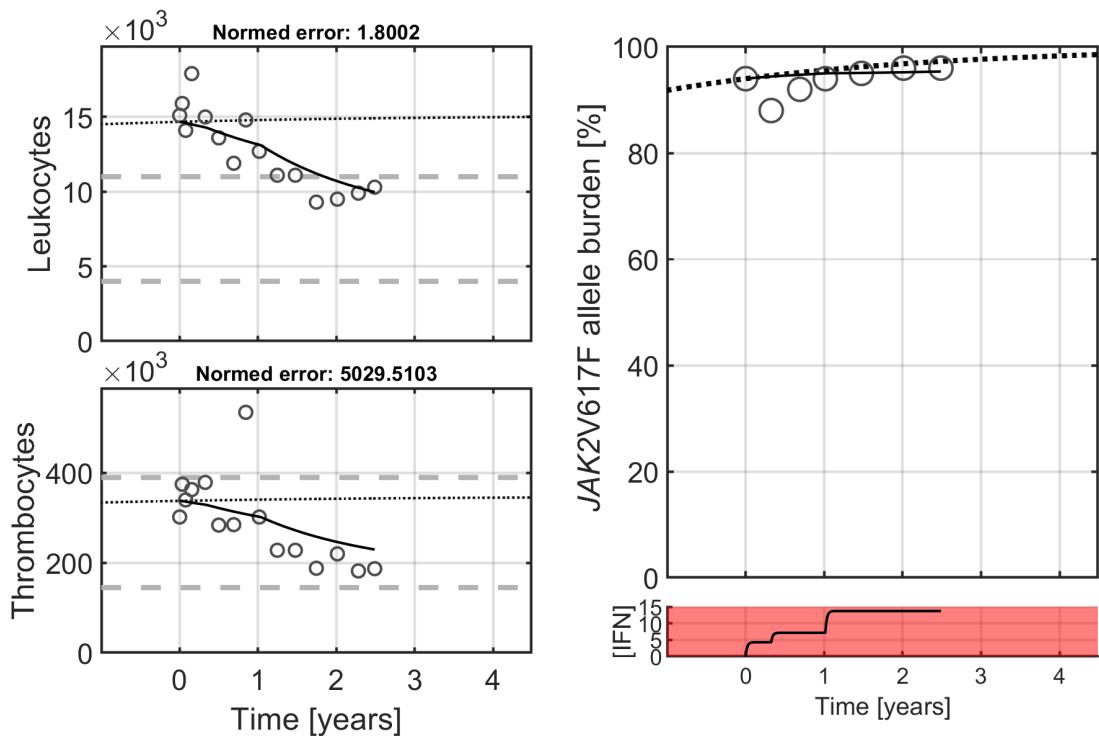
Patient P140



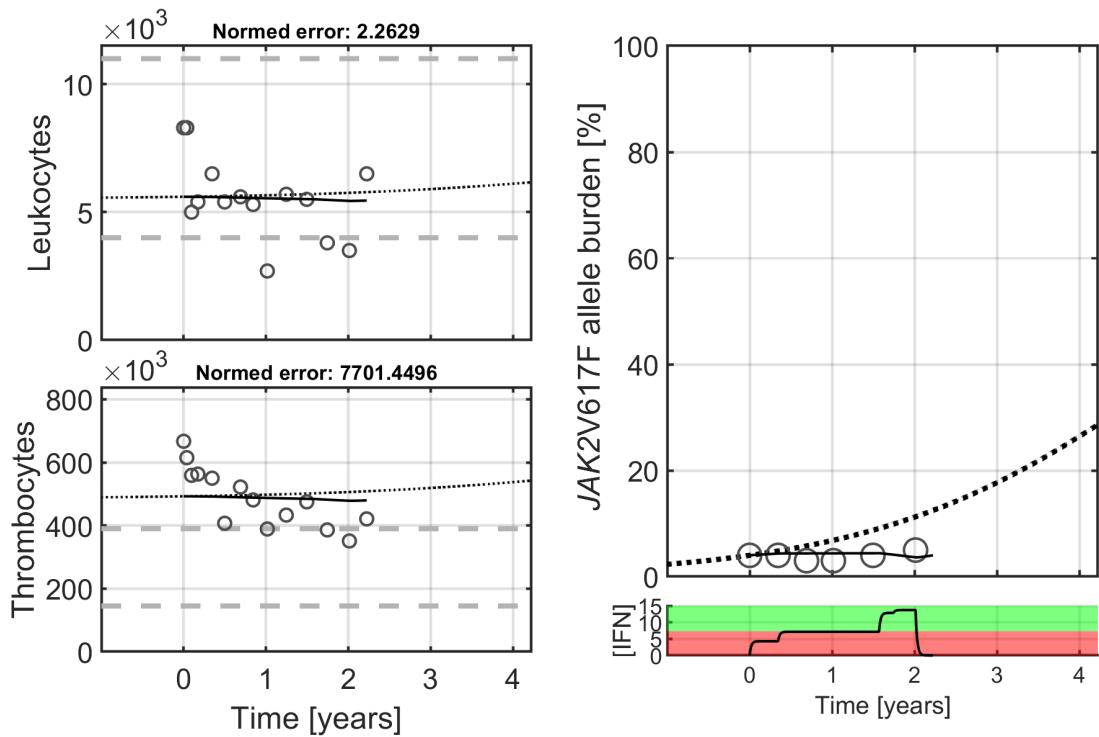
Patient P142



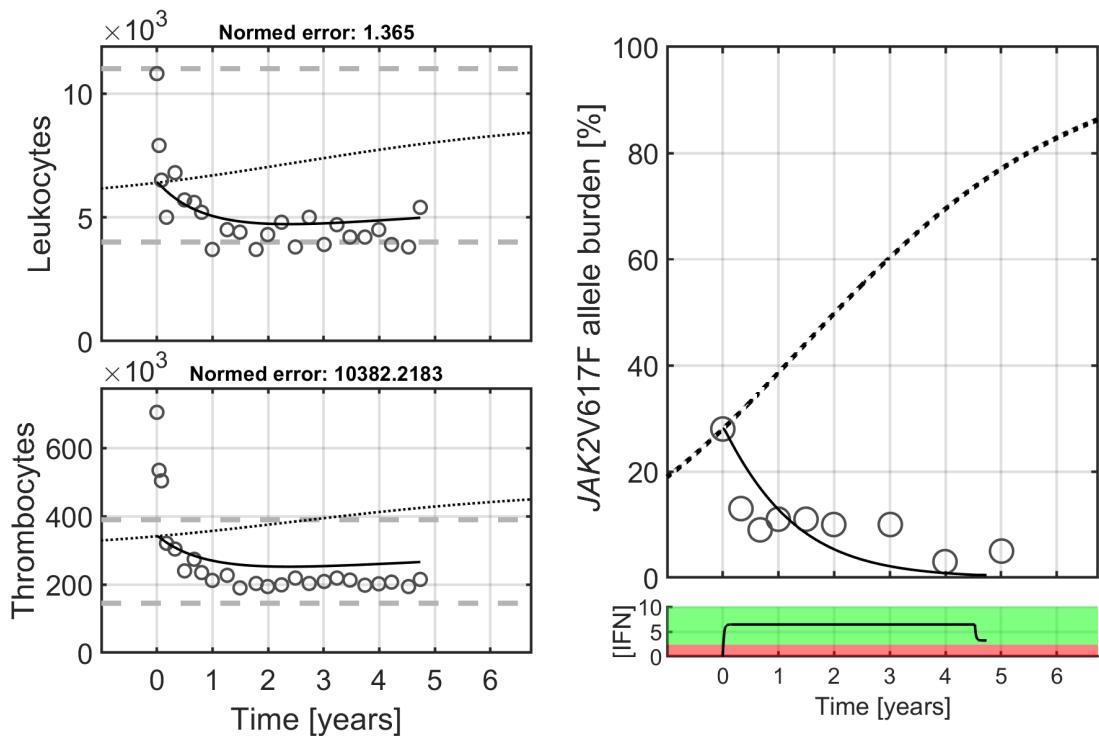
Patient P144



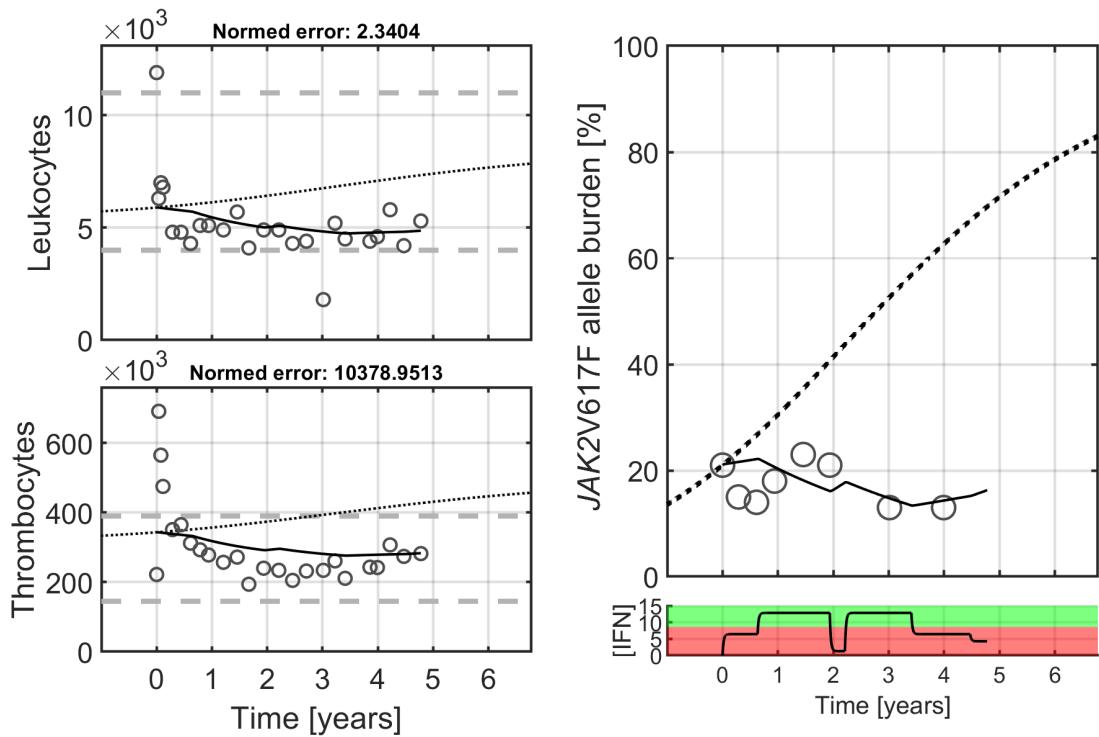
Patient P145



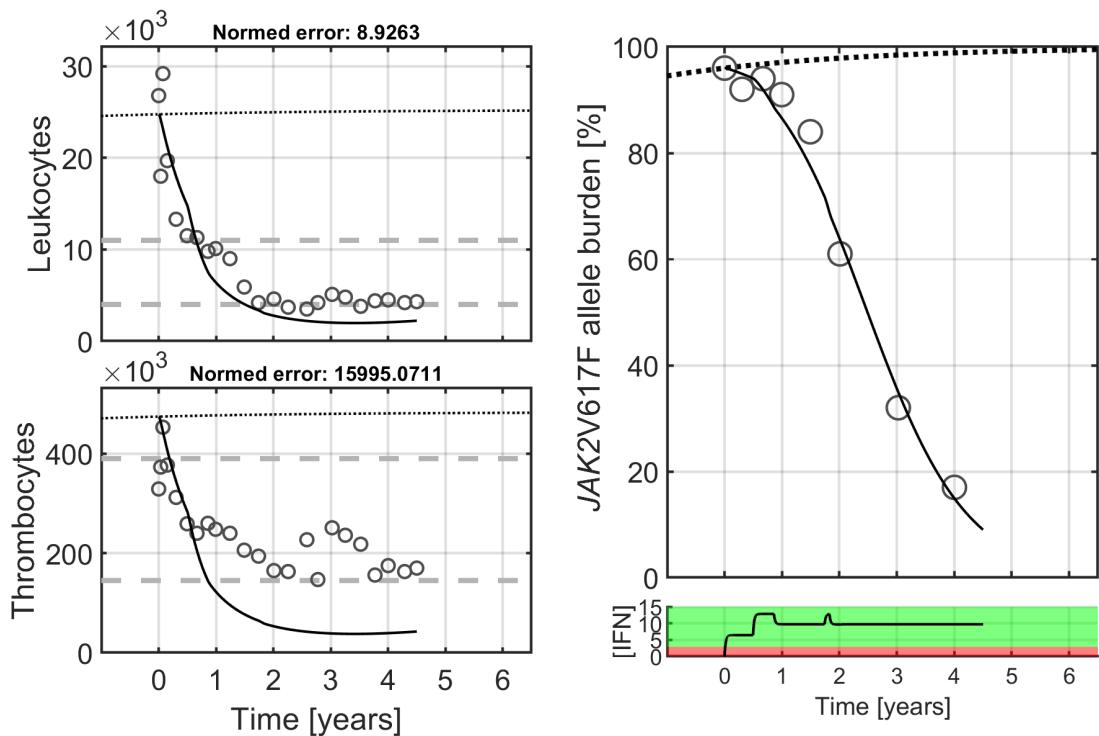
Patient P148



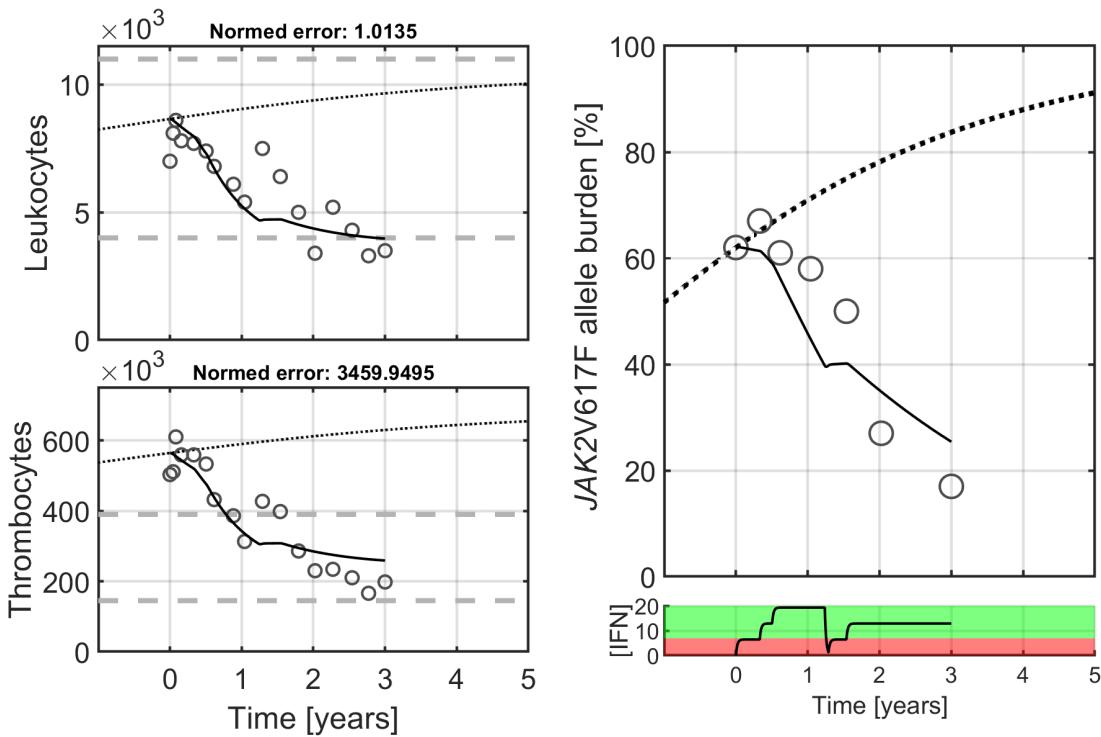
Patient P150



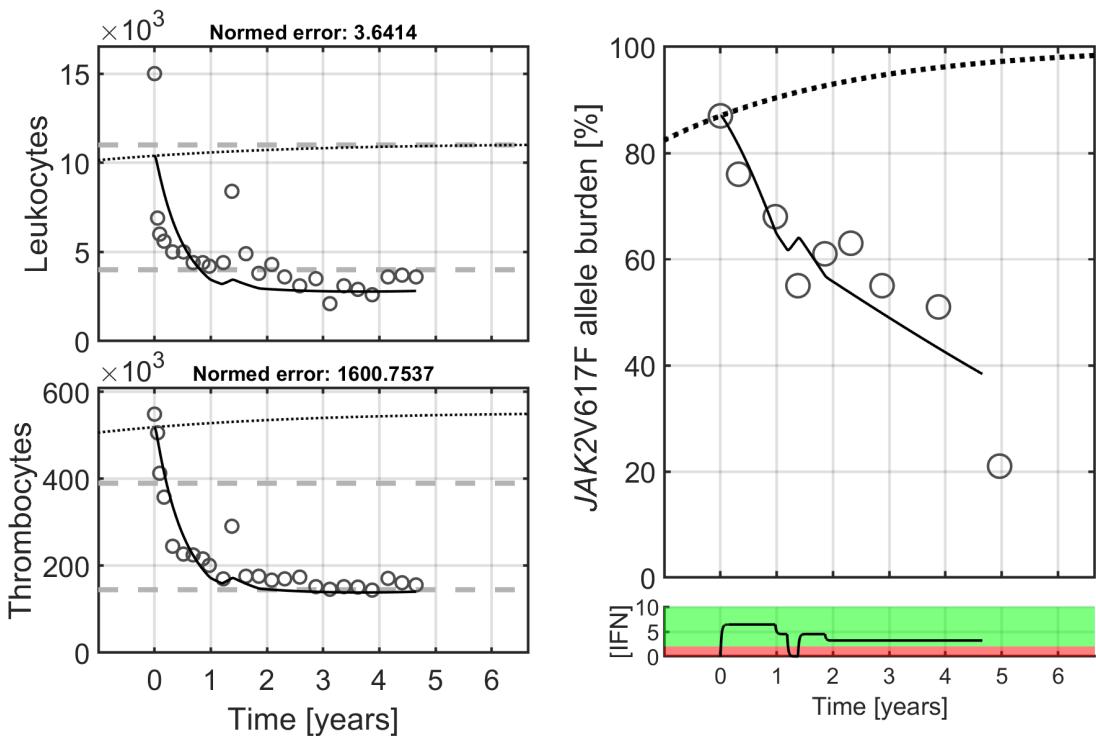
Patient P152



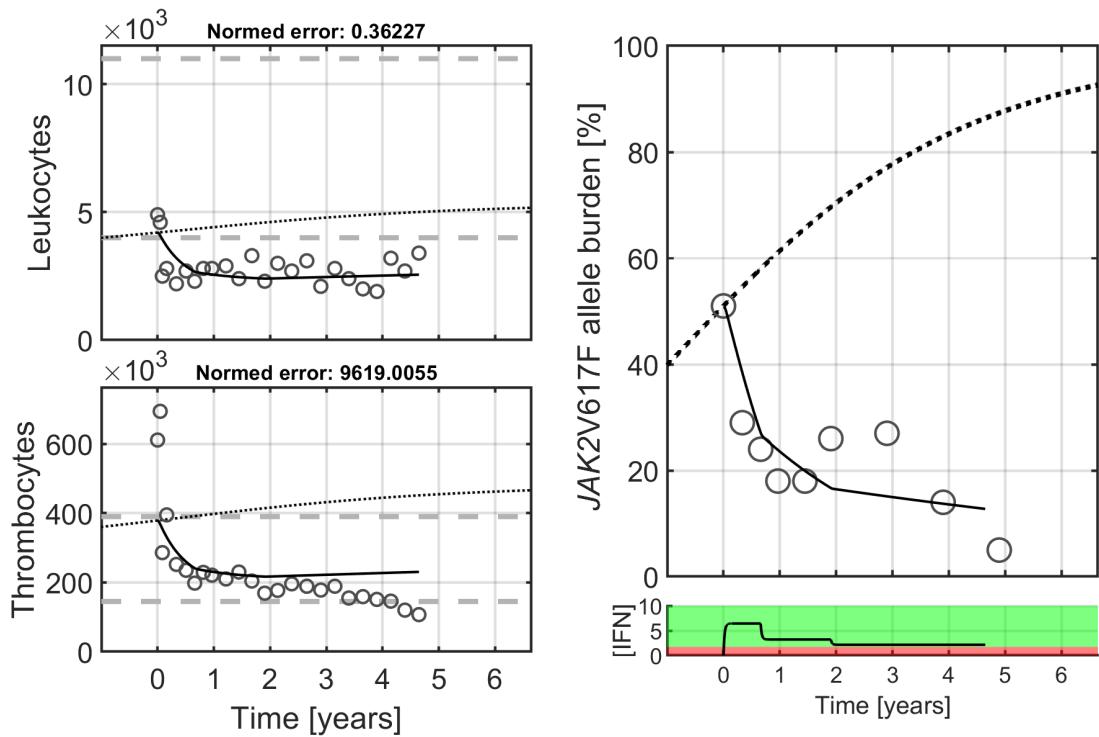
Patient P156



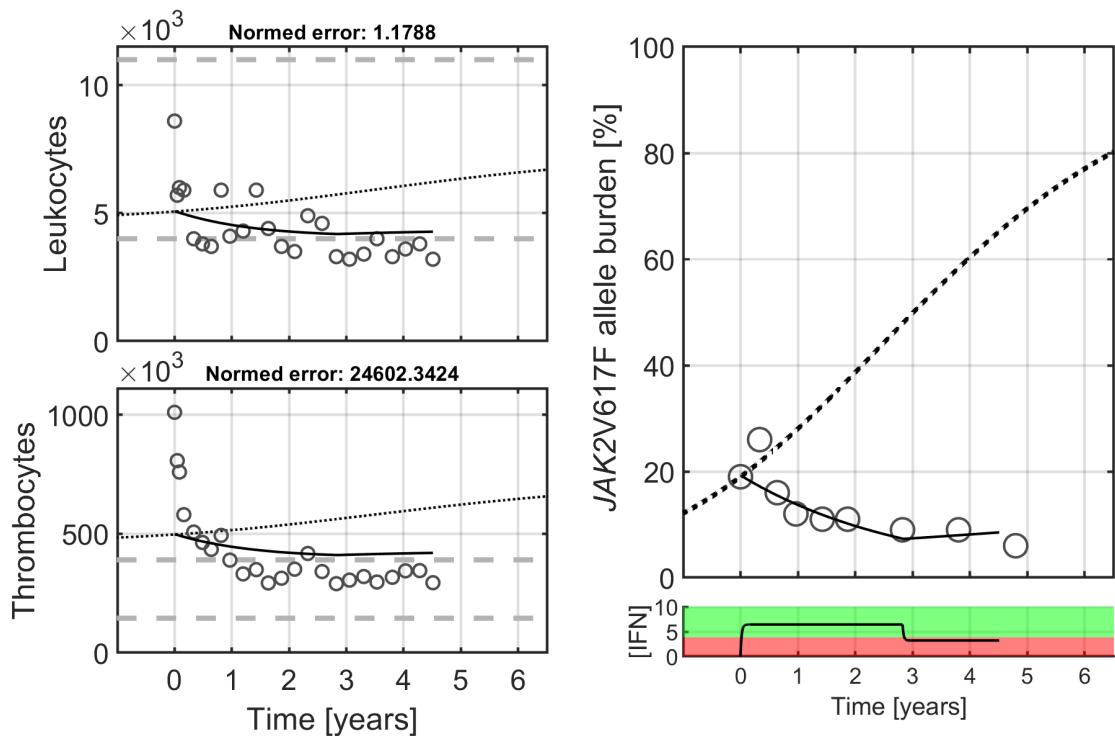
Patient P158



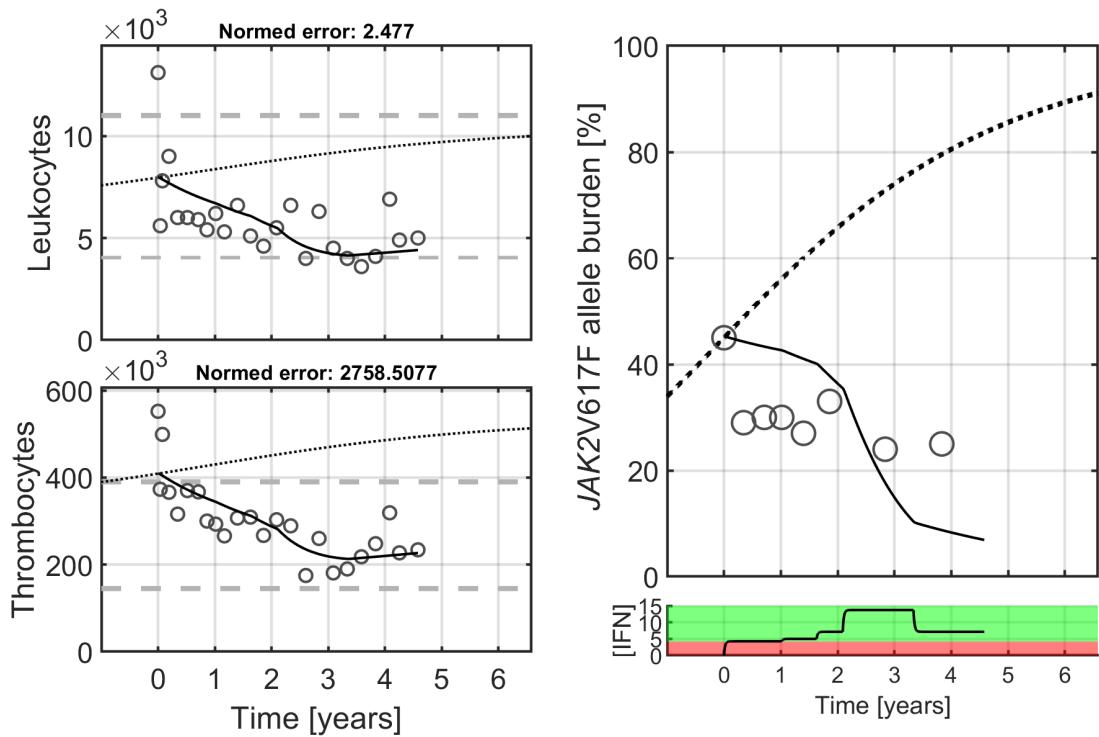
### Patient P162



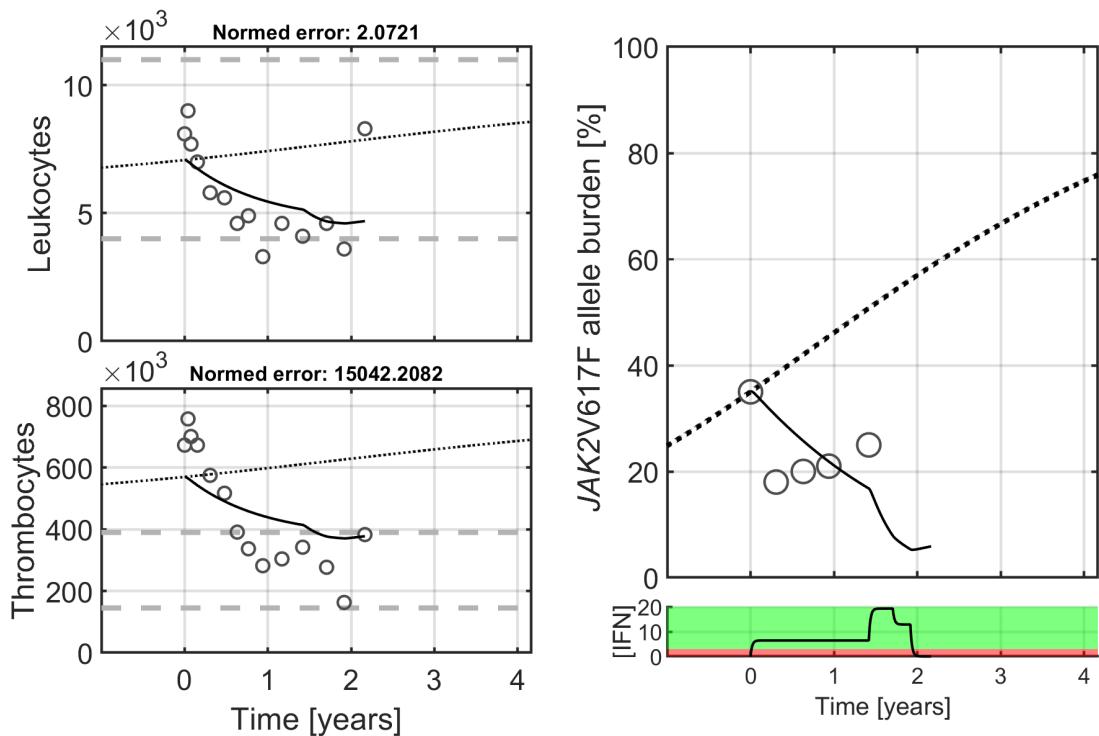
### Patient P163



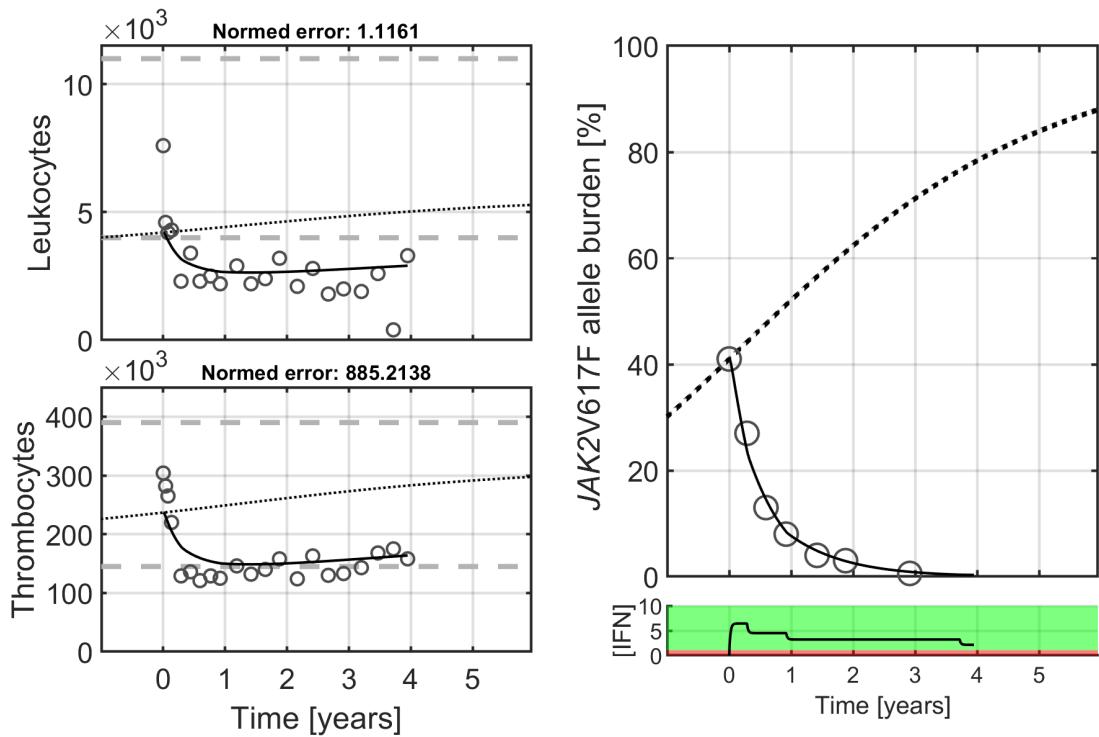
Patient P164



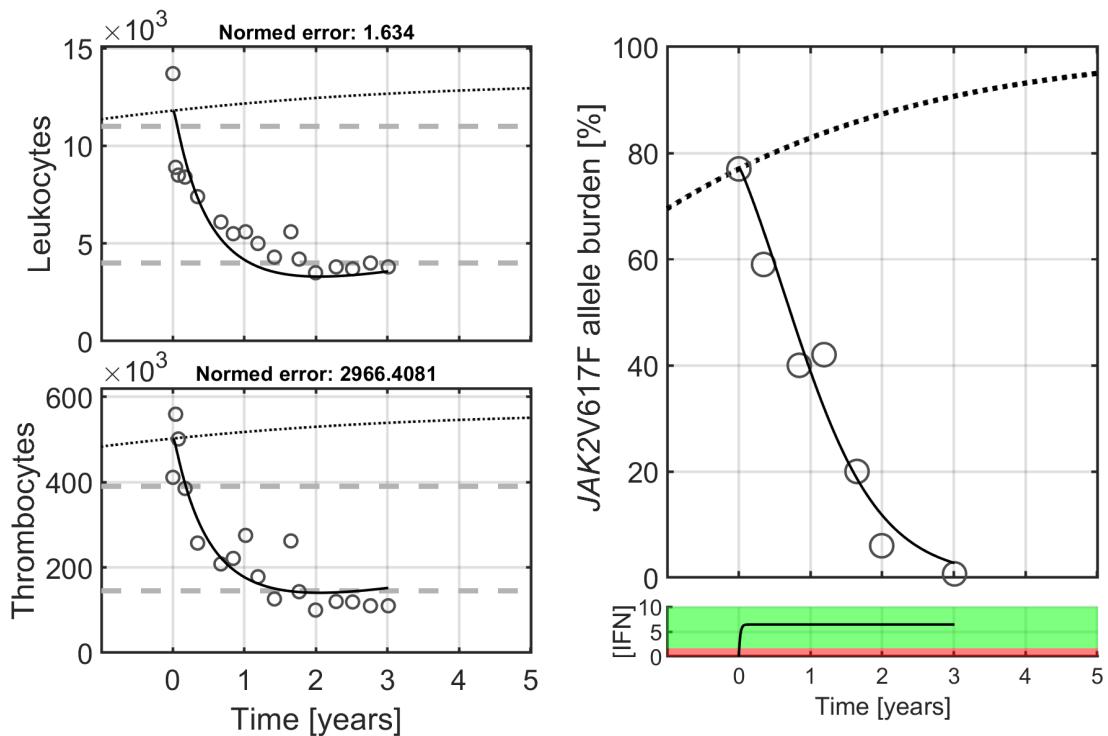
Patient P167

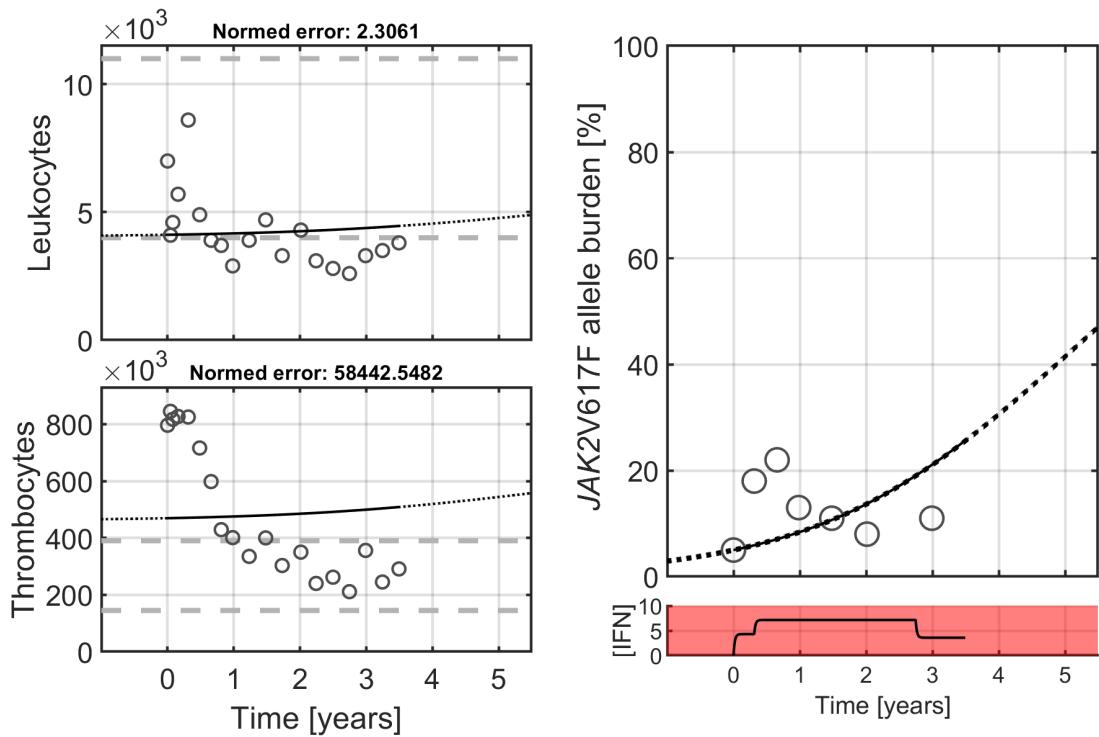
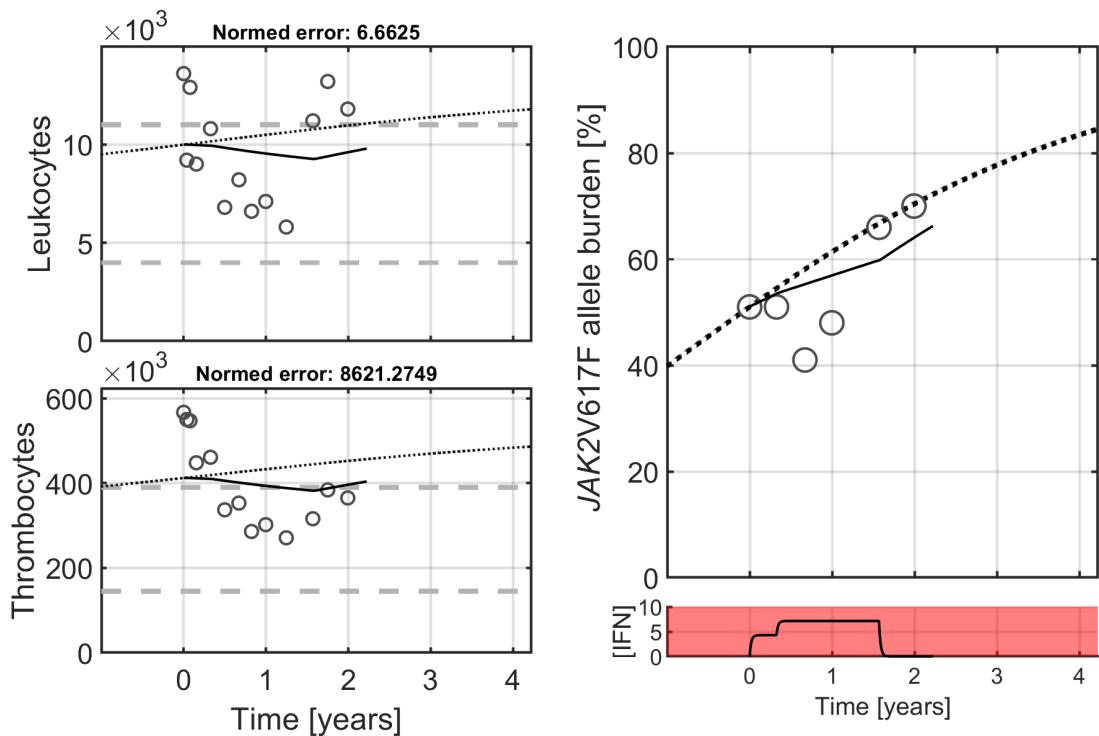


Patient P184

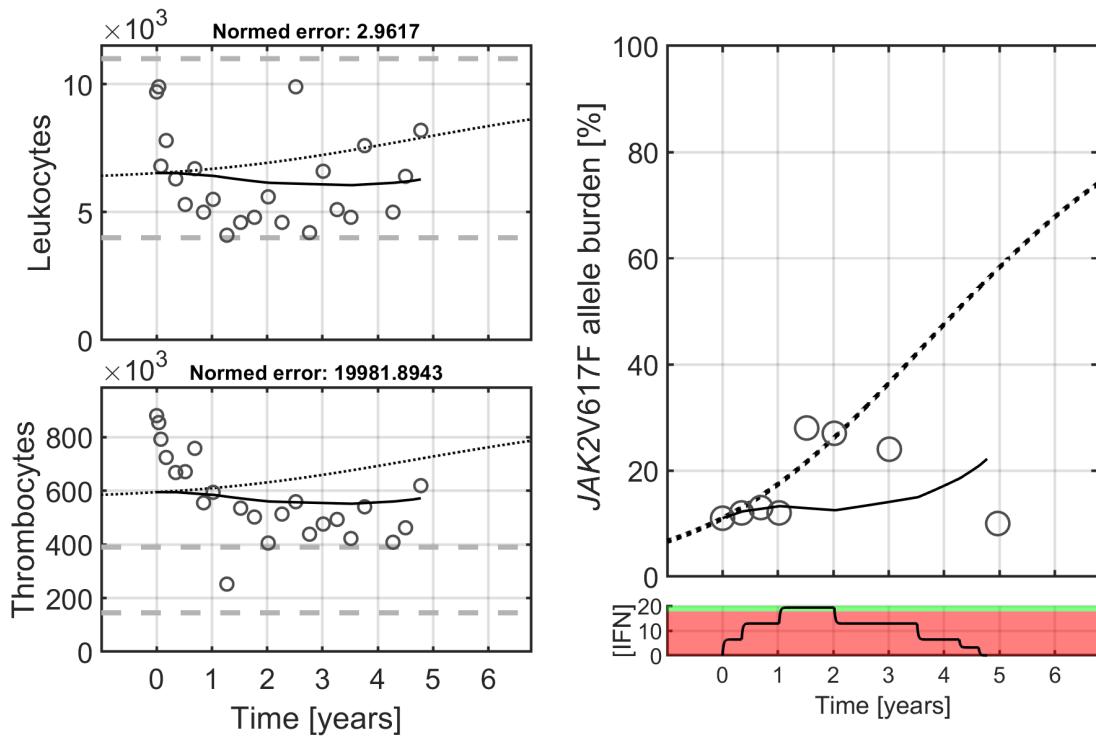


Patient P187

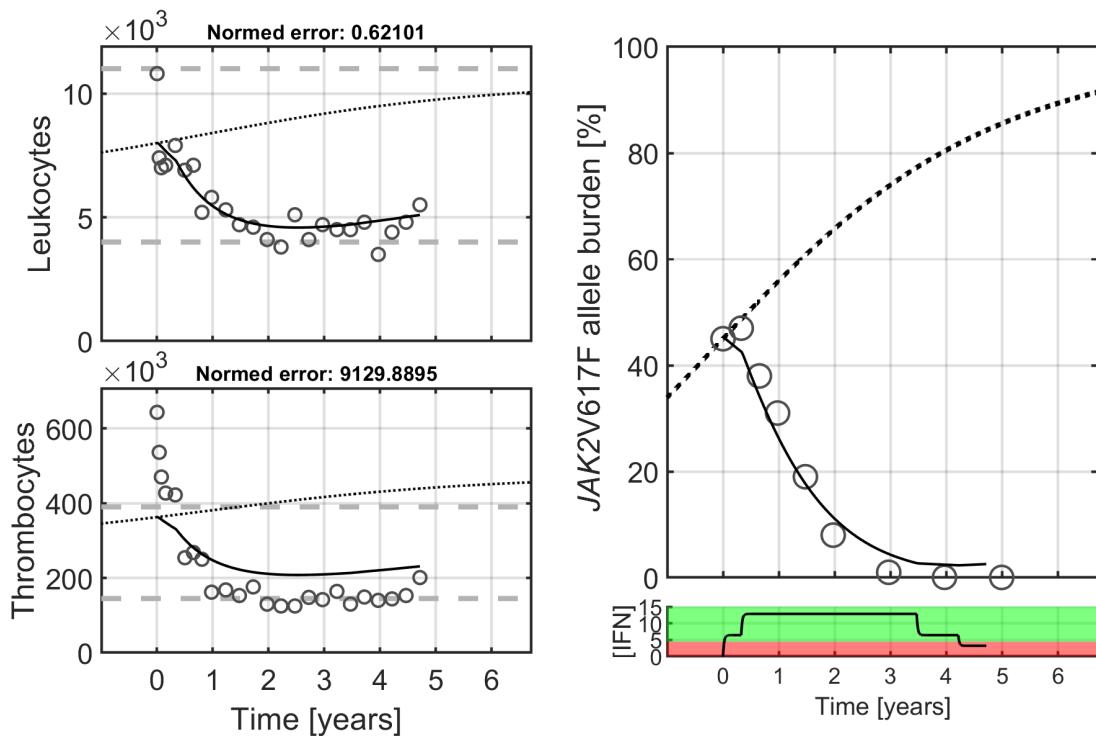


**Patient P190****Patient P196**

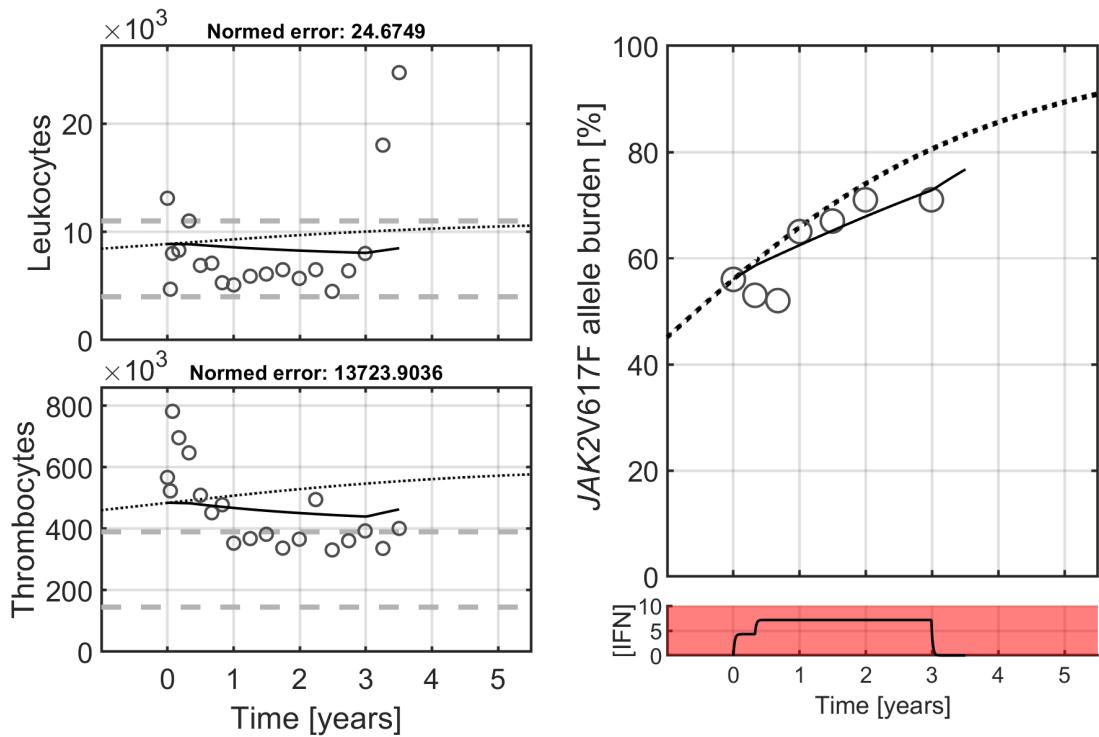
Patient P197



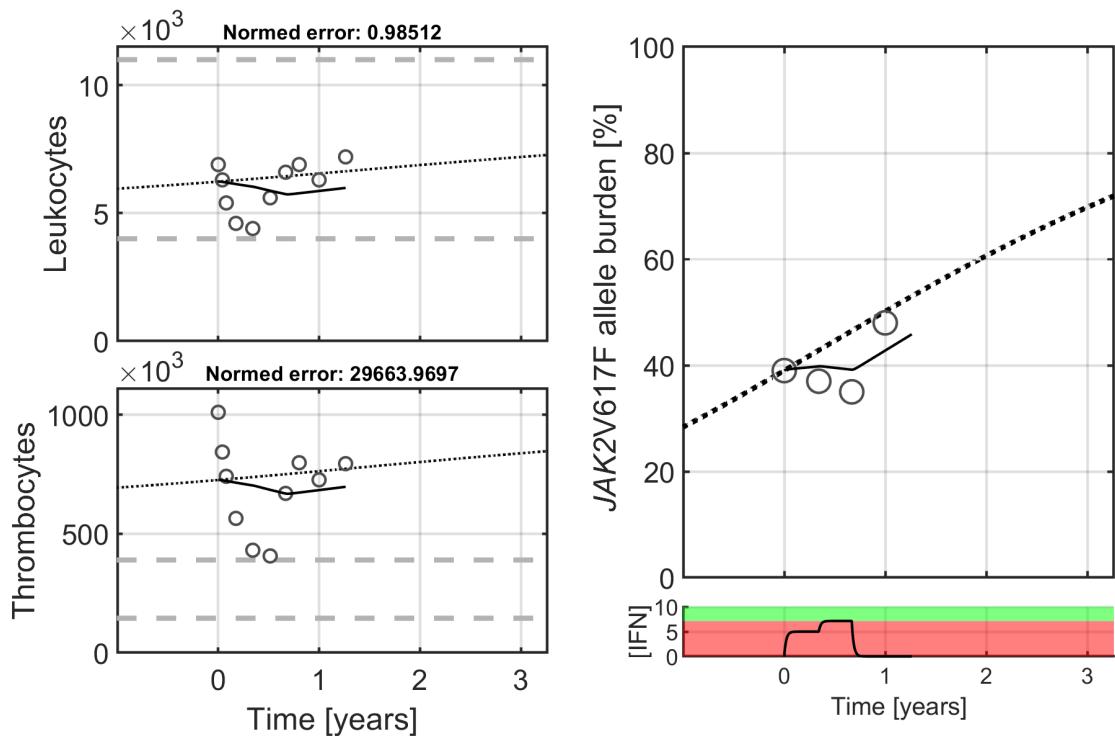
Patient P198

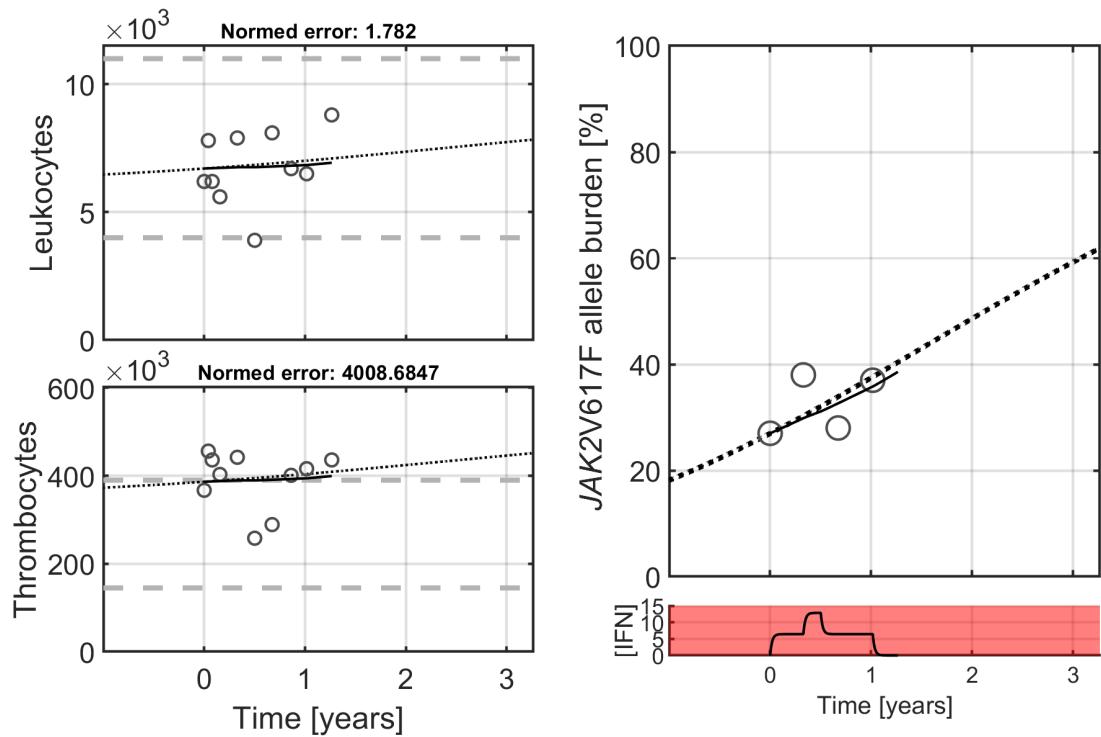
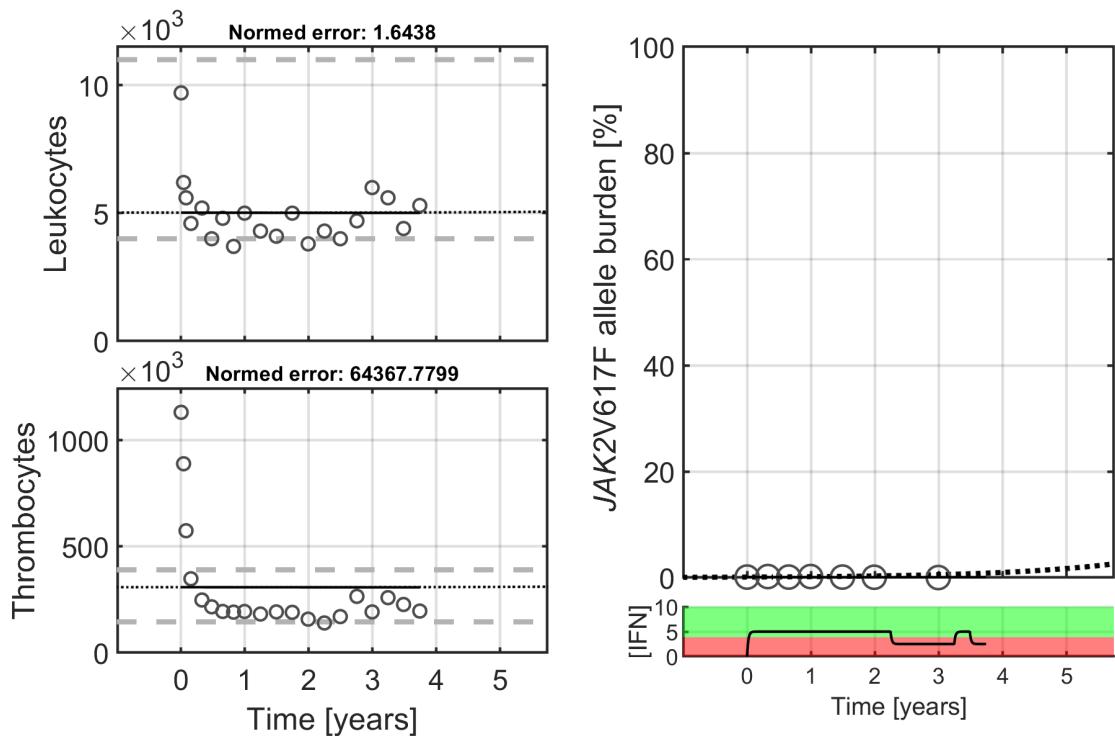


Patient P199

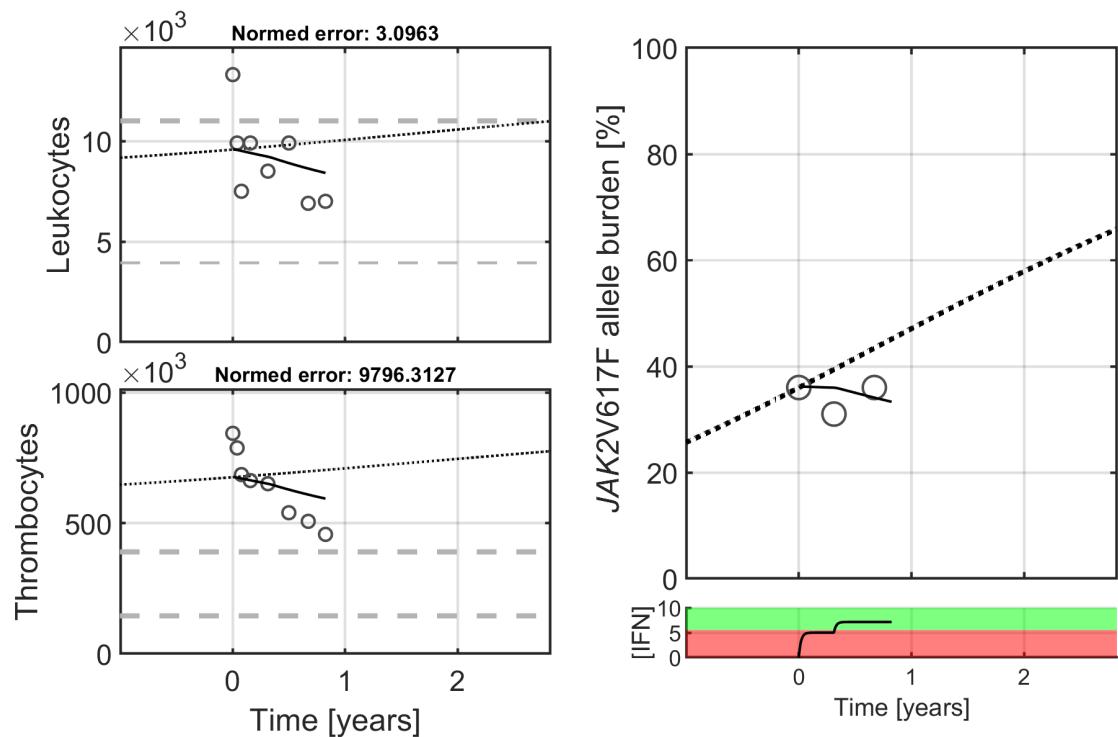


Patient P201



**Patient P202****Patient P203**

Patient P205



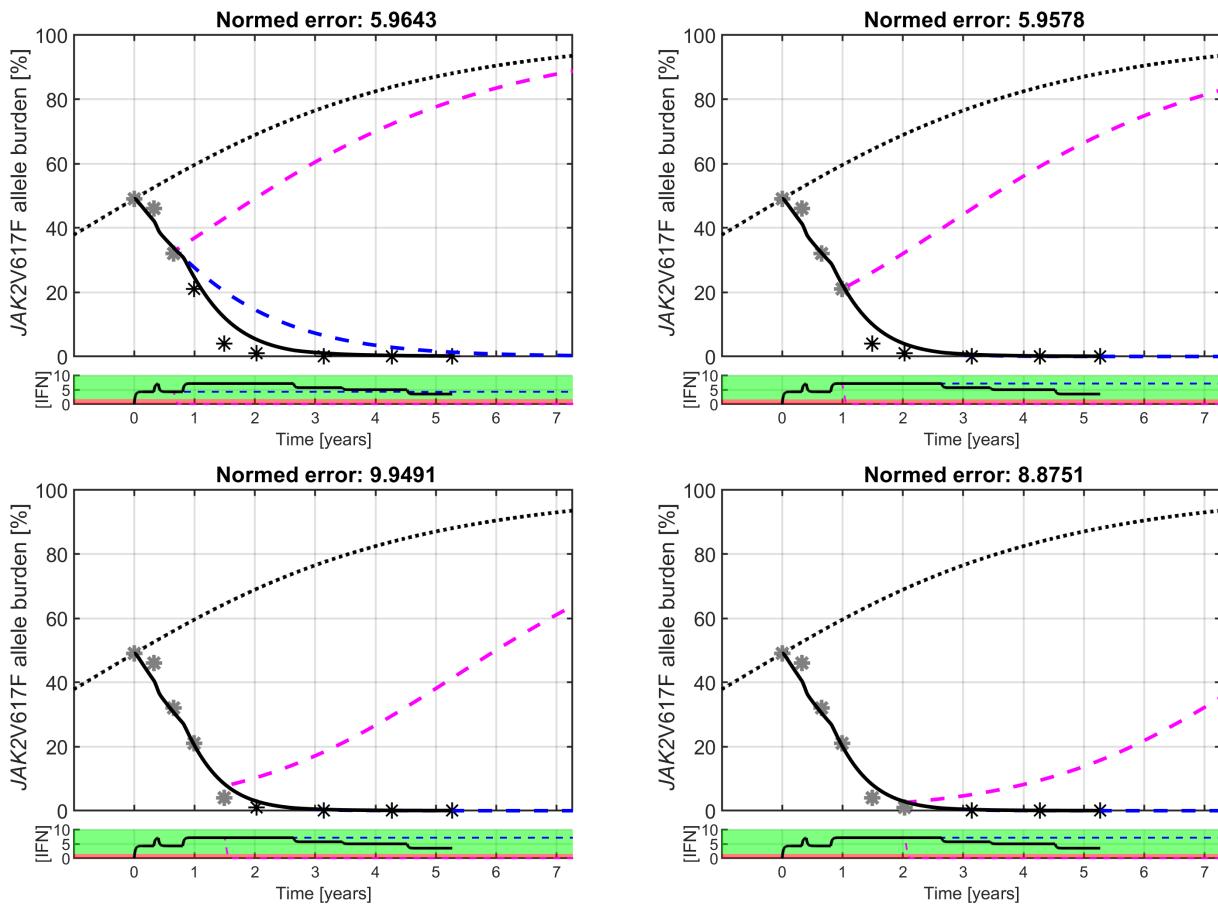
## Supplementary material D: Predictive plots of *JAK2V617F*

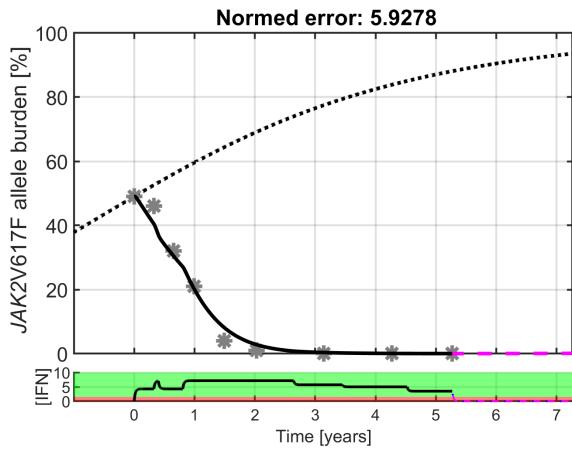
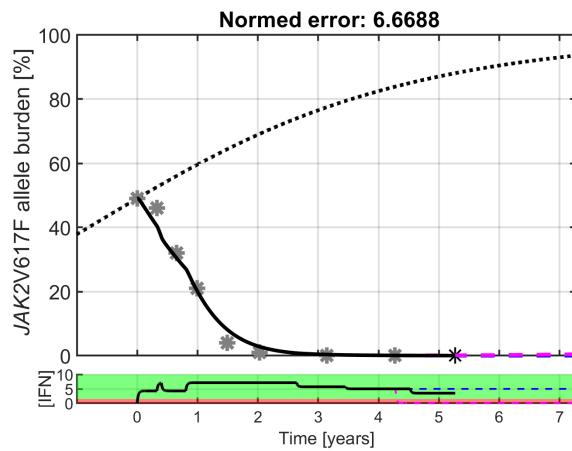
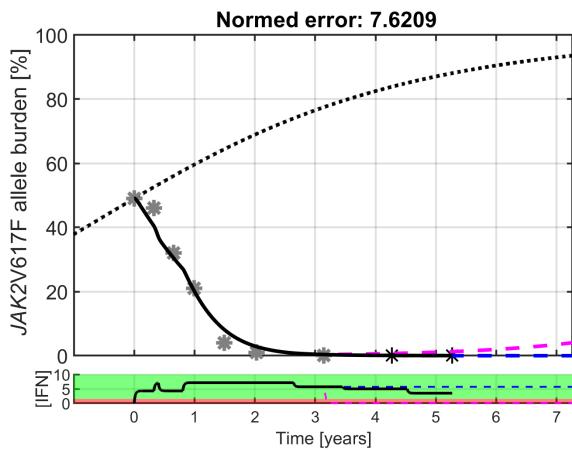
In this supplementary material, we show figures similar to those shown in supplementary material B. The only difference is that here predictions of continued treatment is also considered.

The full black curves show the model prediction following the actual real dosing, as in supplementary material B. The blue and pink curve displays the hypothetical model predictions for difference dosing schedules, see the bottom panels. The blue curve displays a dosing schedule where the current treatment at the last grey data-point is continued (i.e. if the patient was administered an average daily dose of 5  $\mu\text{g}$  of IFN at the last data-point used in the fit, the simulation is continued with 5  $\mu\text{g}$  of IFN indefinitely). The pink curve displays the model prediction of a treatment-stop scenario, in which treatment is discontinued after the last grey data-point. As total extinction of malignant stem cells is only approached asymptotically, treatment-stop will always lead to future disease growth in the model. If the malignant stem cell counts are sufficiently low however, the time before symptoms arise can be far longer than the average life-span. The bottom panels show both the PK-modelling of the blood-concentration of IFN based on the actual dosing, as in Supplementary Material B, as well as the modelled hypothetical concentrations. The color-coding corresponds to the upper panel, with blue displaying an unchanging dose and pink displaying a treatment-stop scenario.

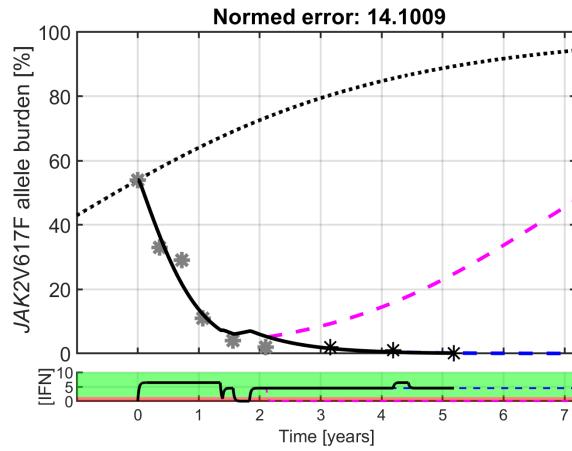
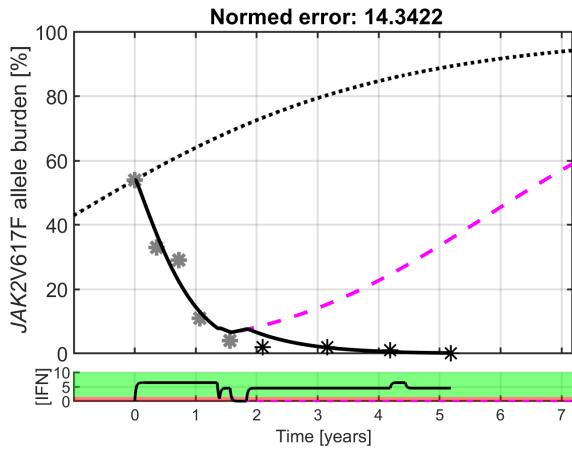
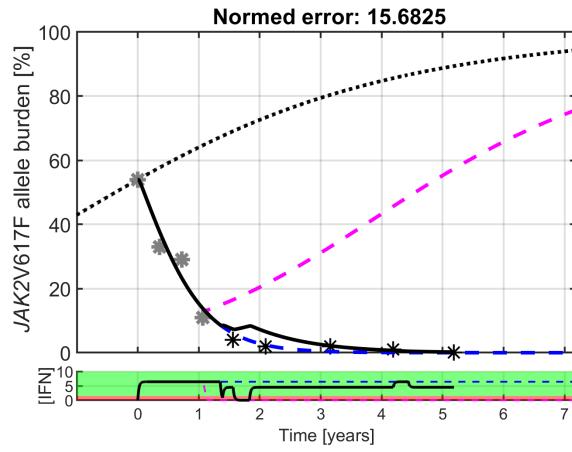
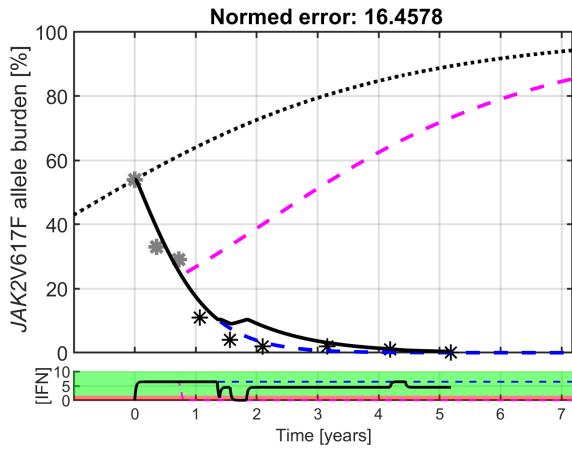
At the top of all figures, a goodness-of-fit-metric of the best fit is shown, defined as the sum of squared errors, divided by the number of points used in the fit. A low number signifies a good fit. Only the error of points used (the grey points) were included in the error estimate.

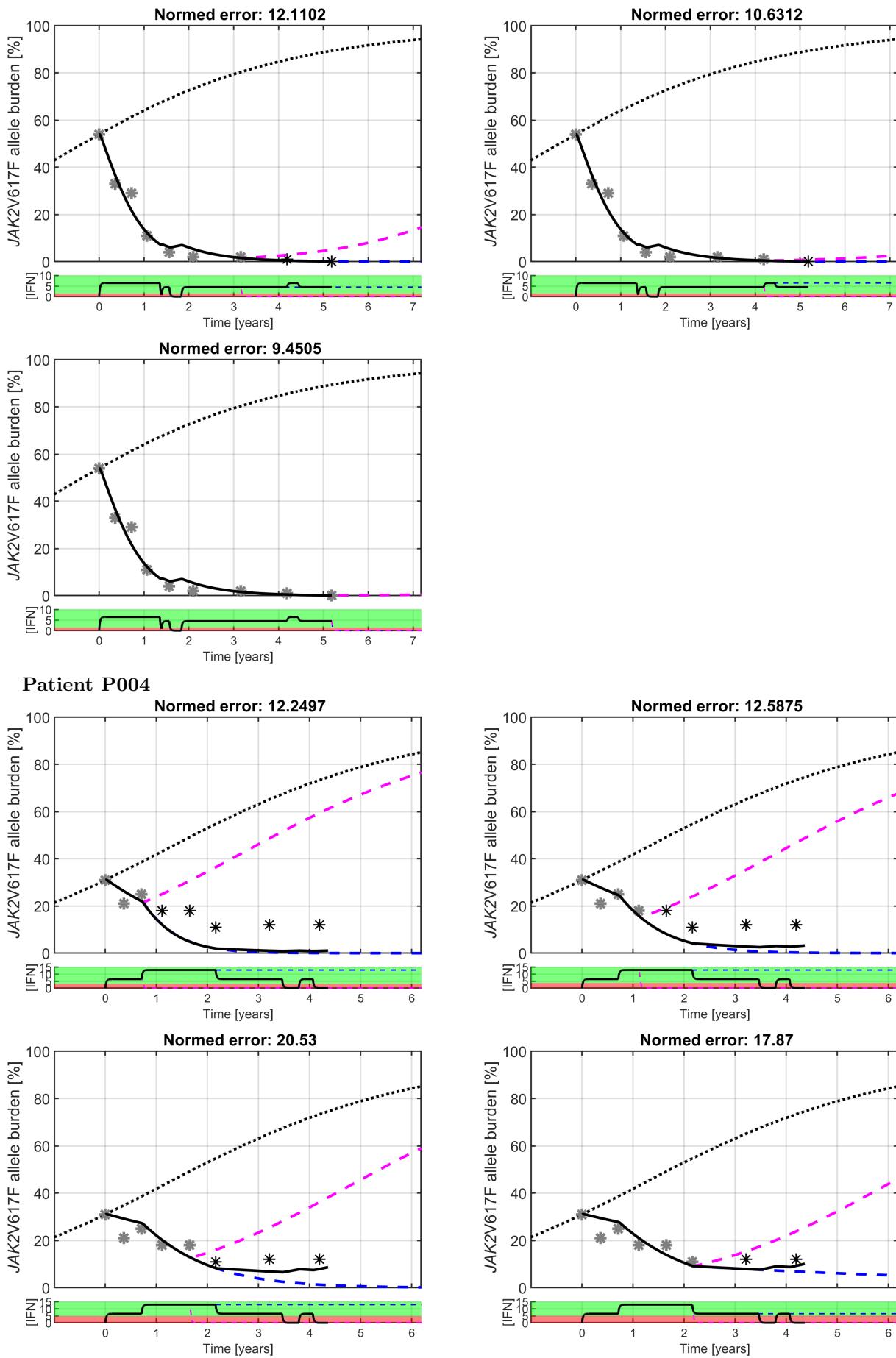
Patient P002

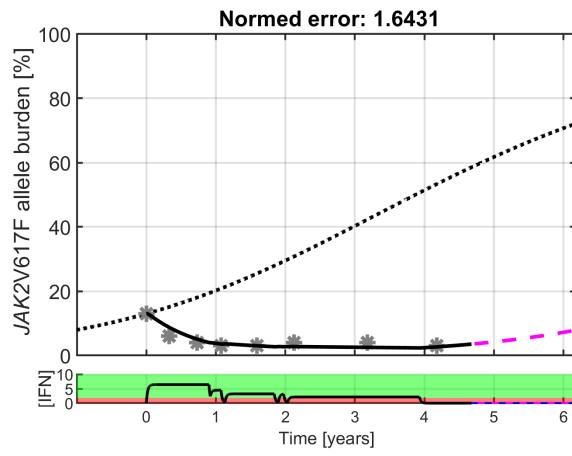
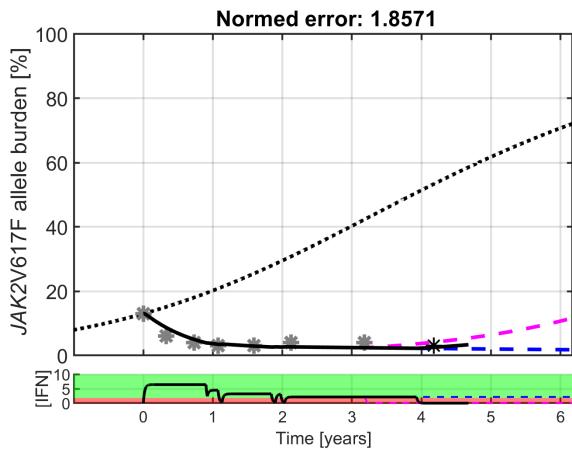
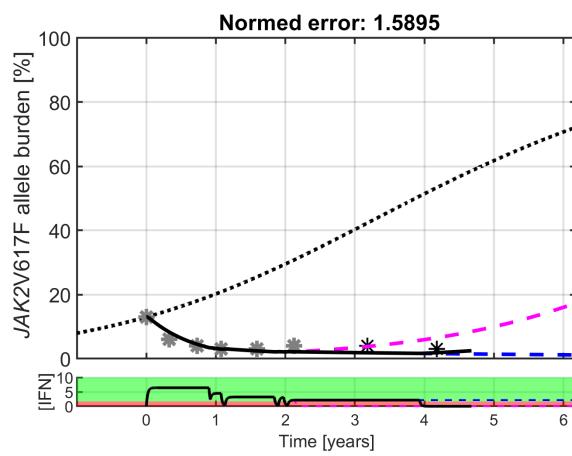
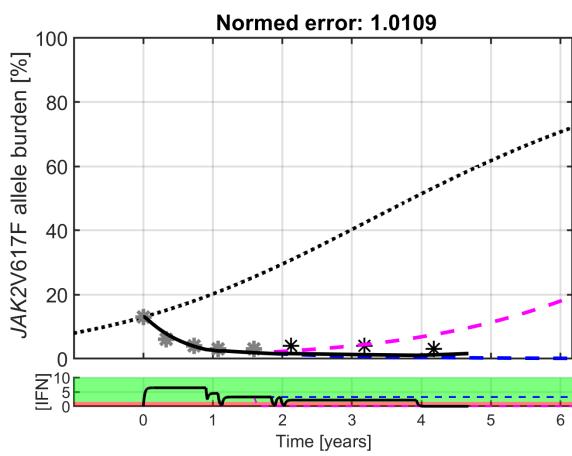
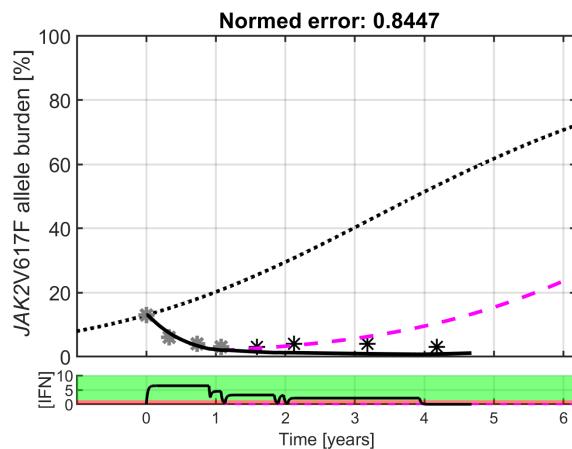
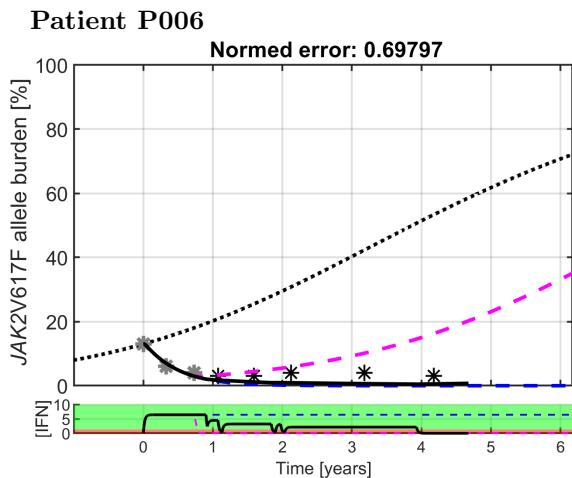
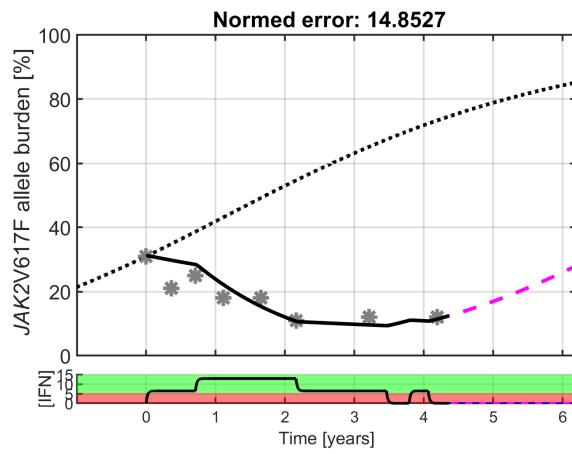
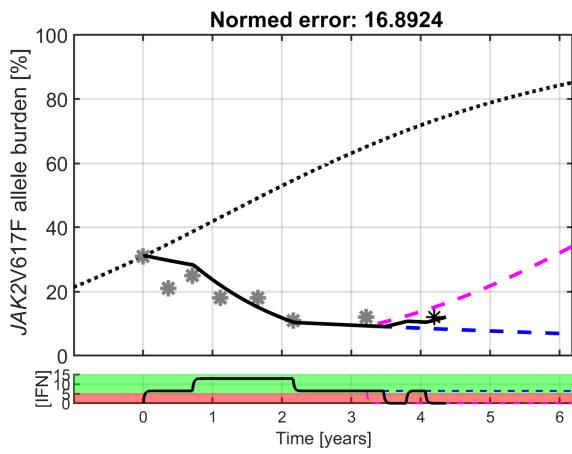




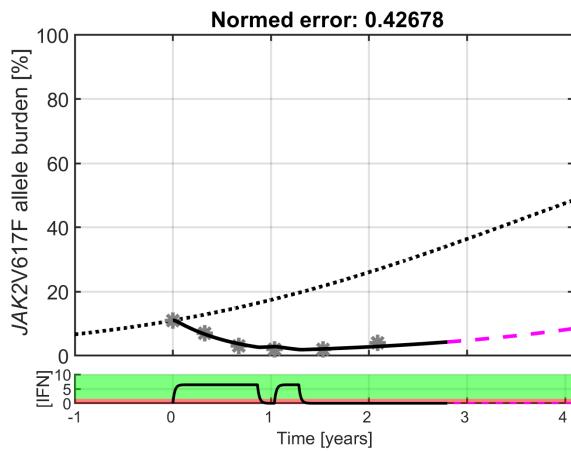
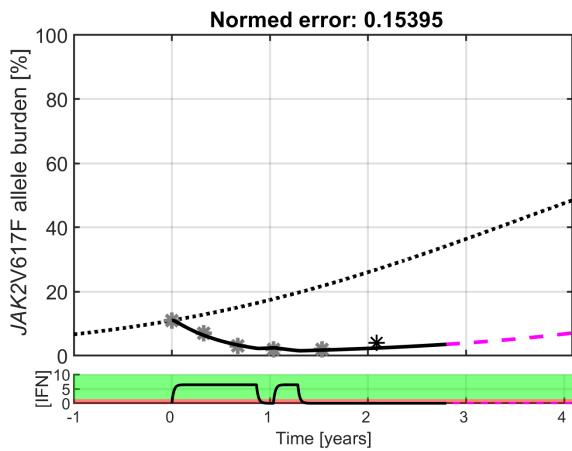
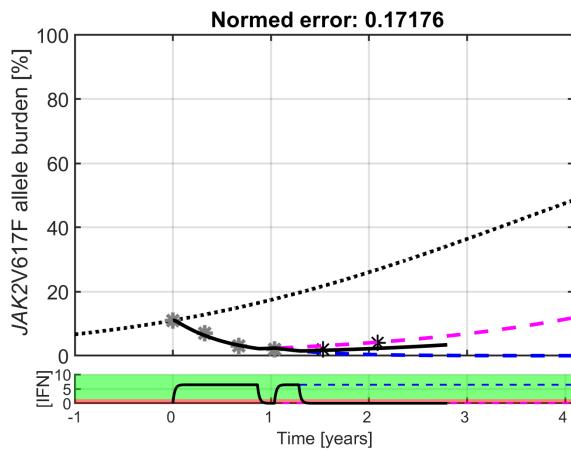
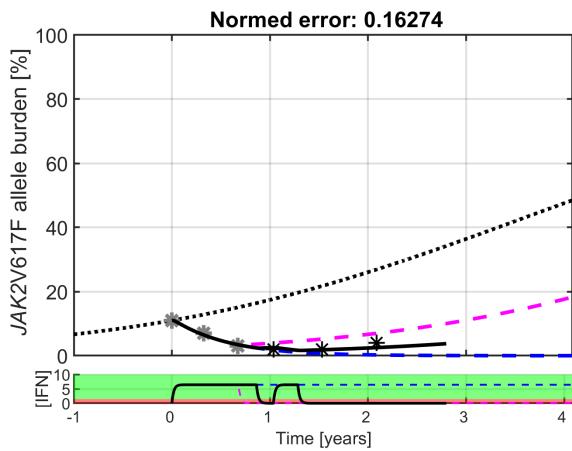
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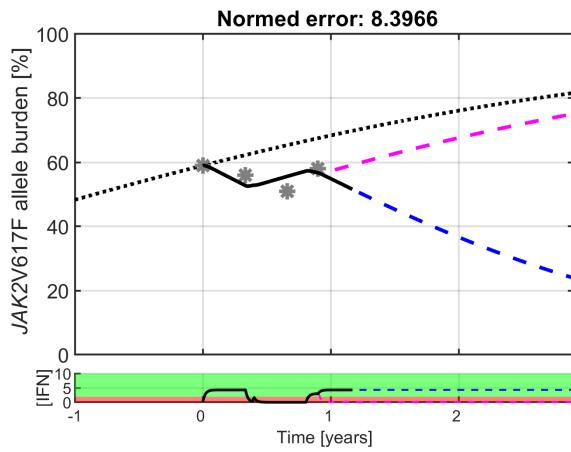
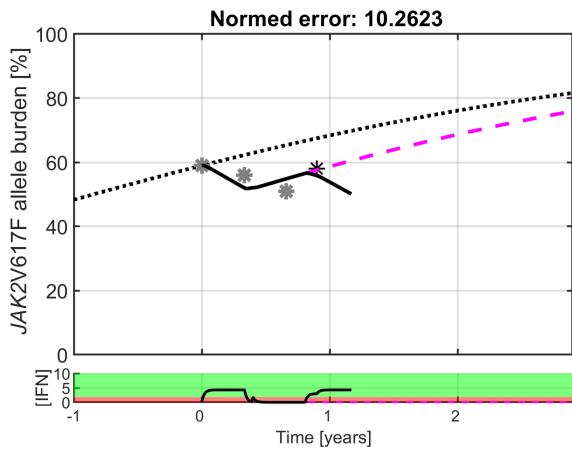




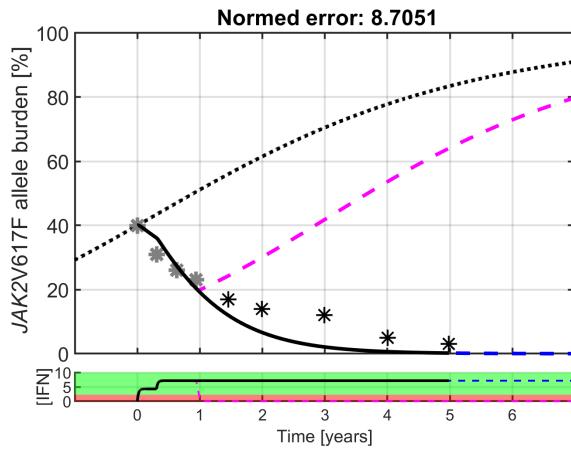
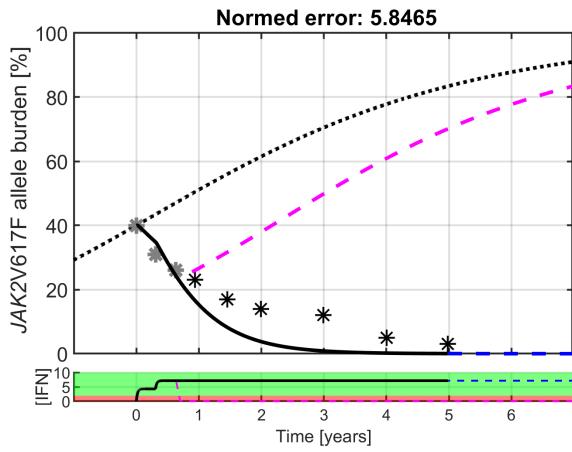
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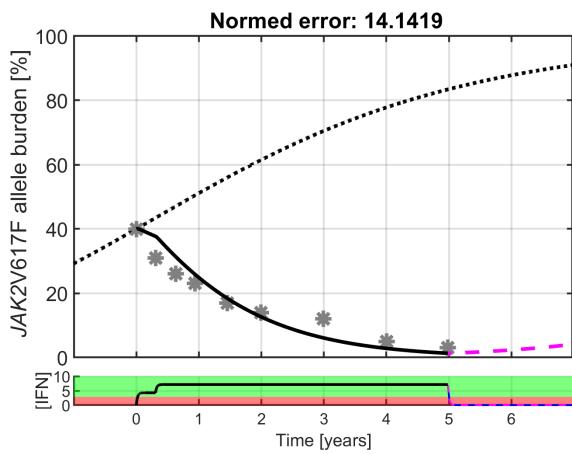
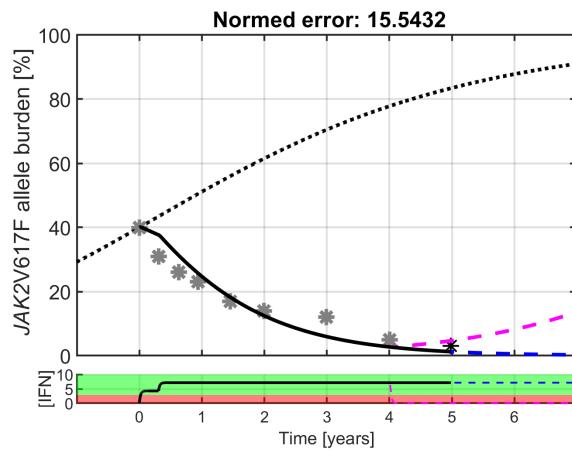
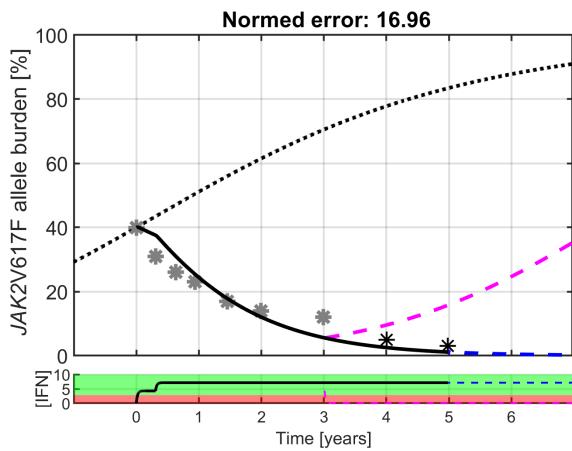
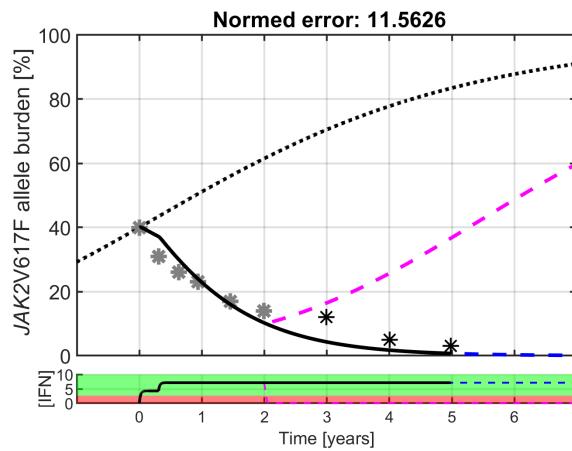
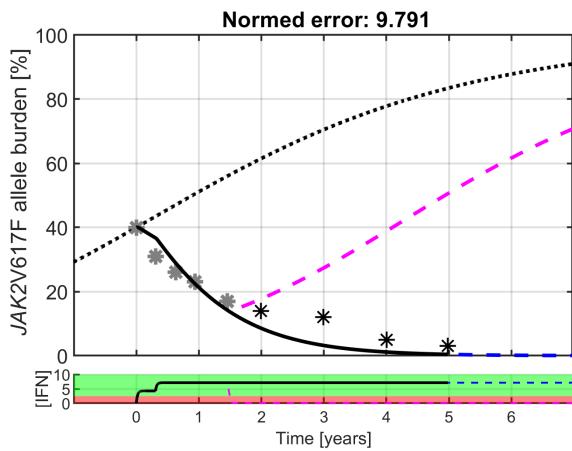


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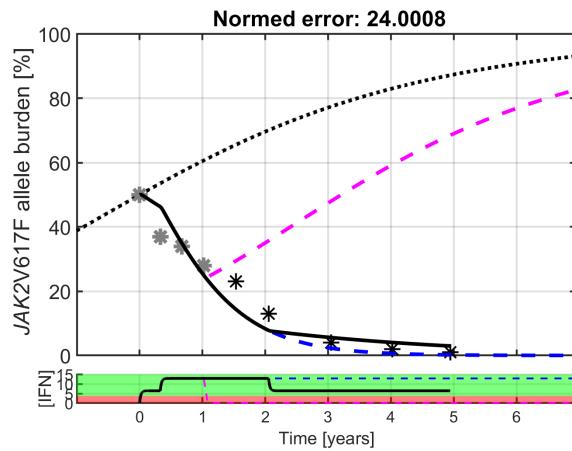
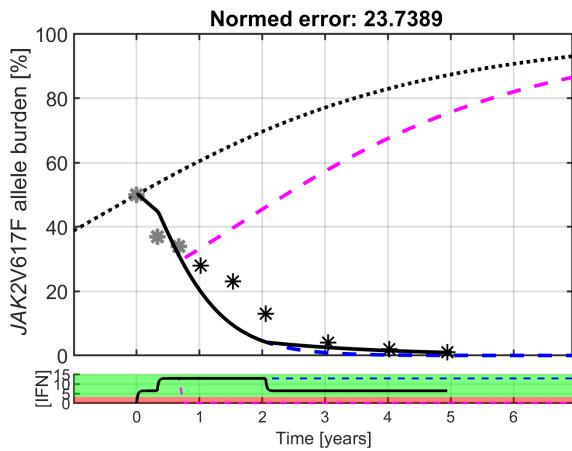


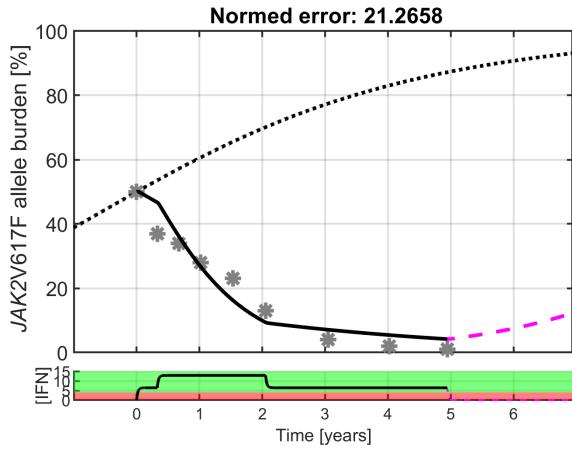
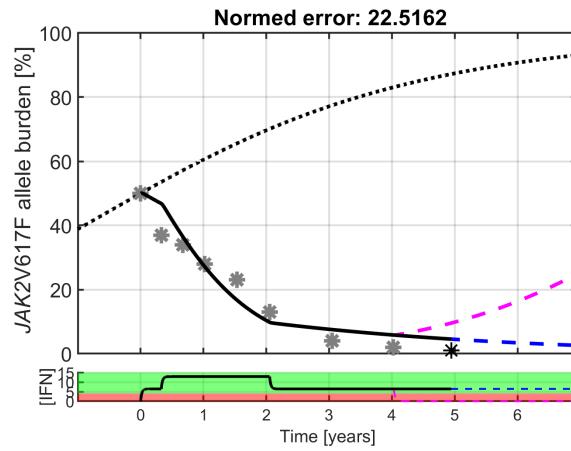
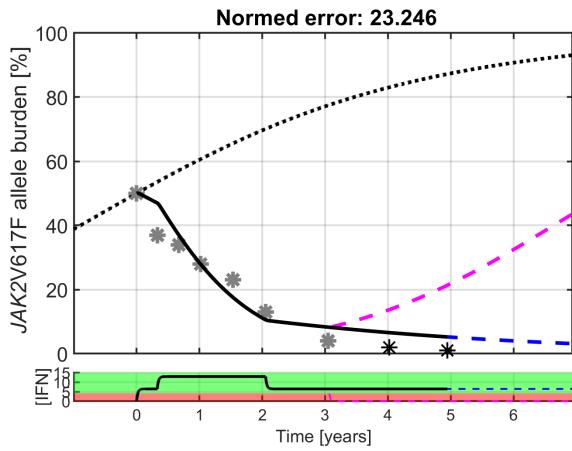
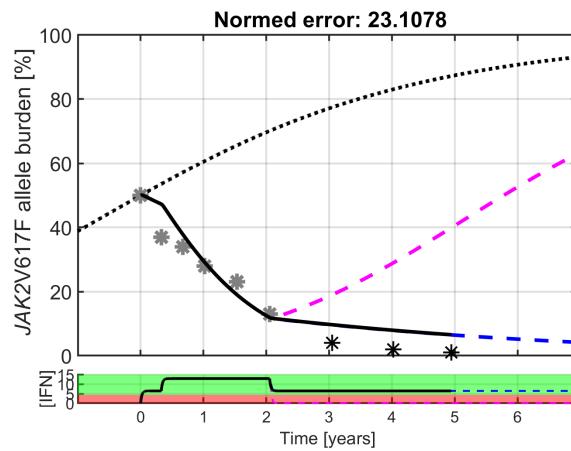
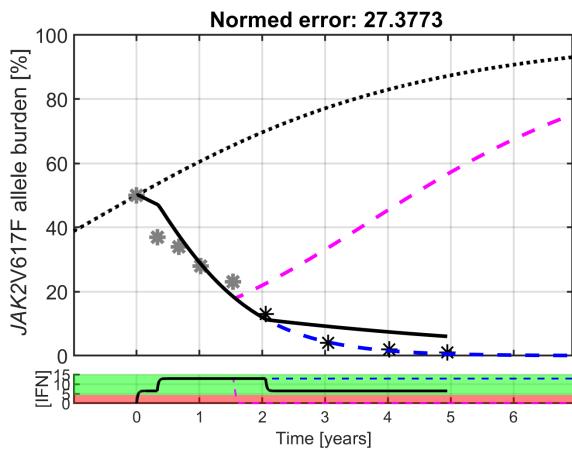
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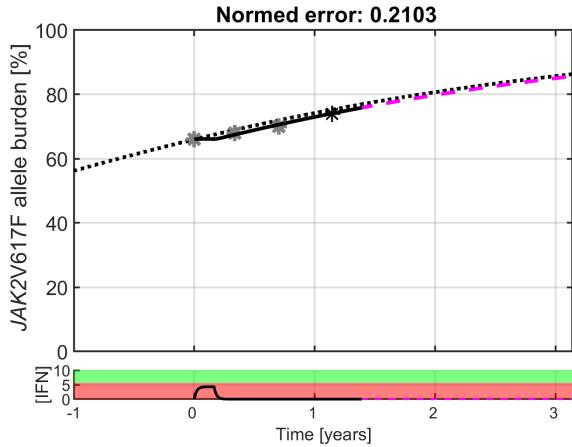


Patient P021

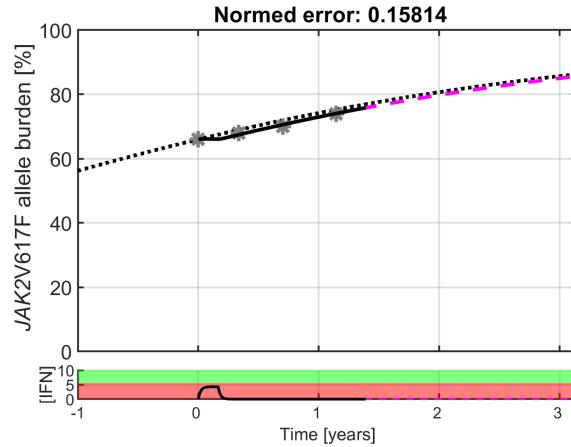


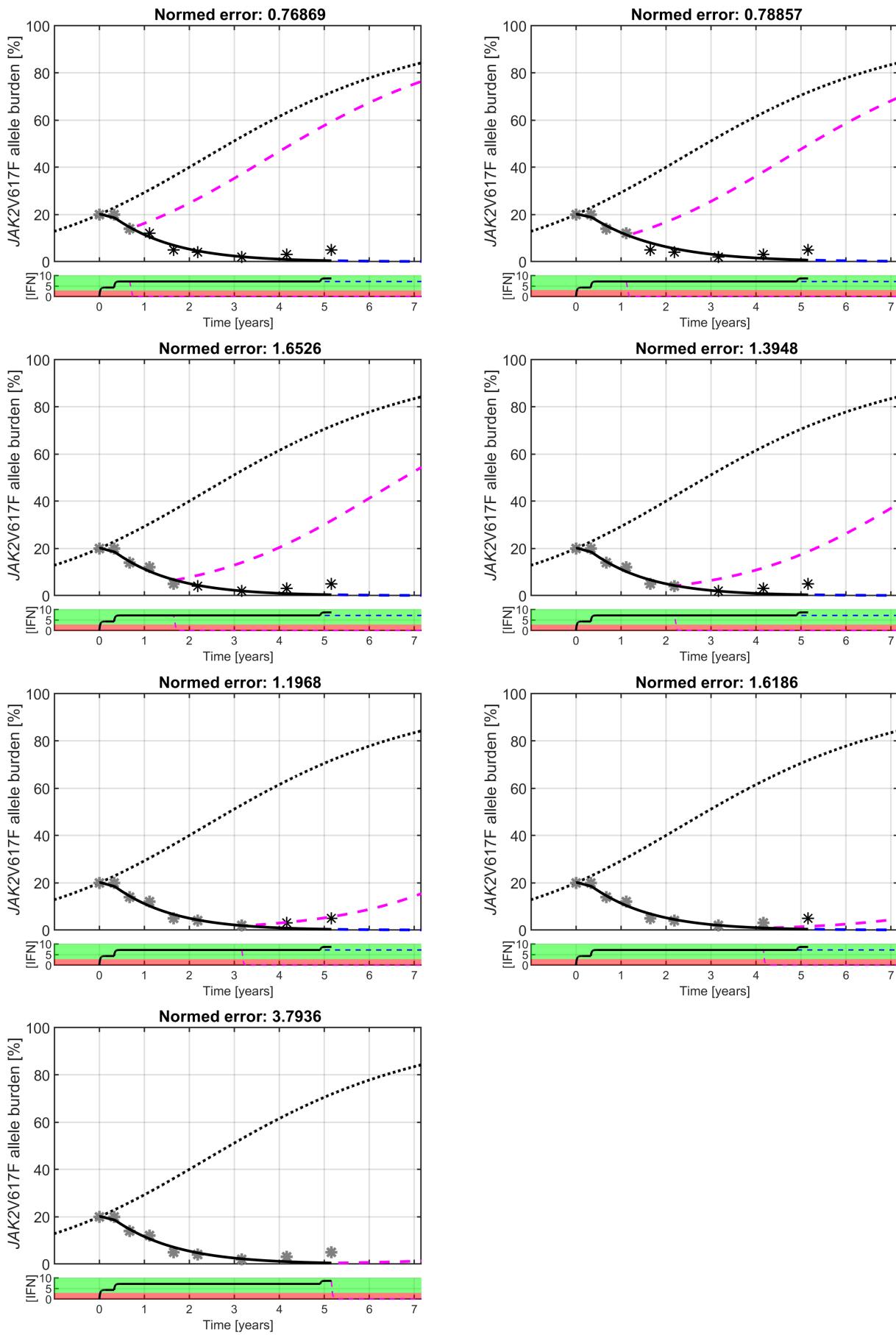


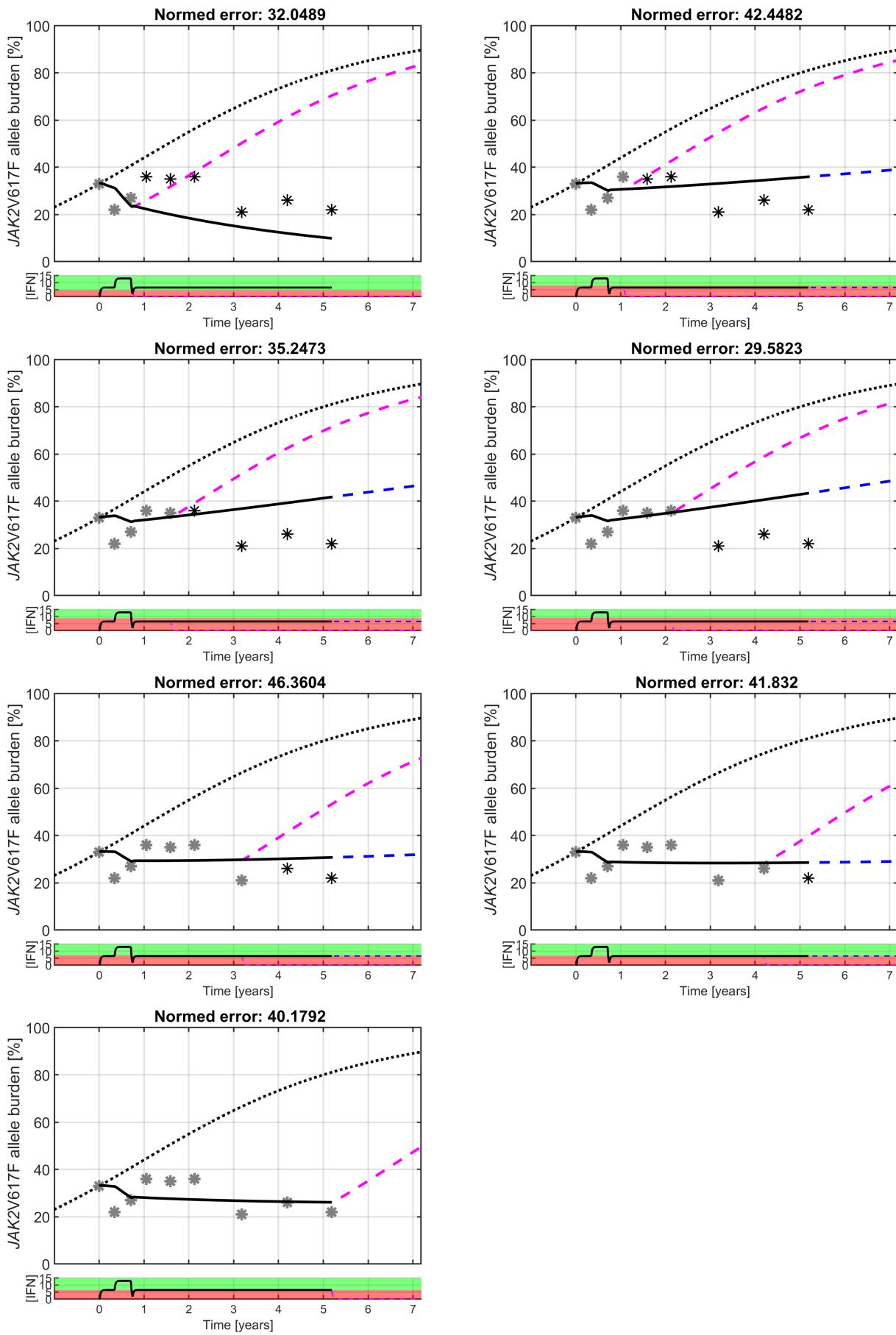
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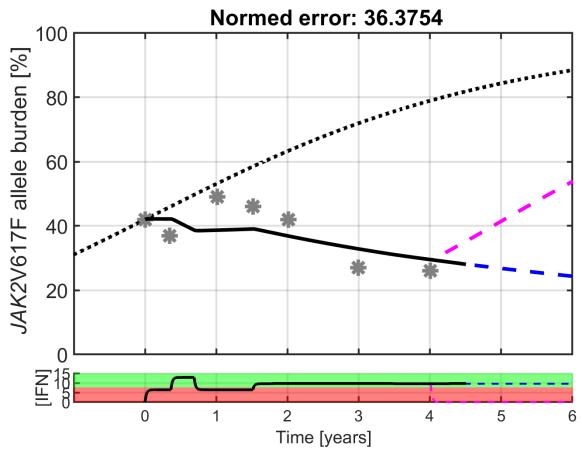
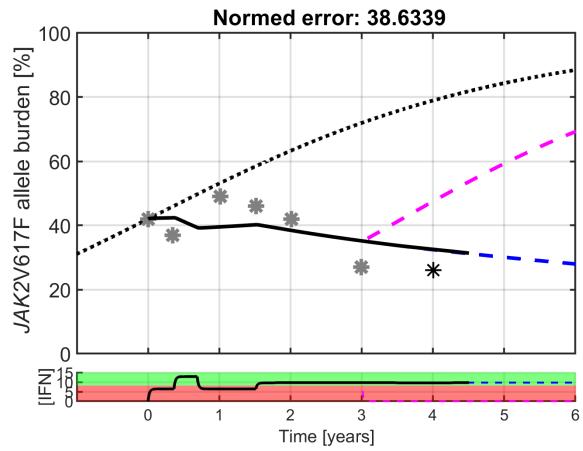
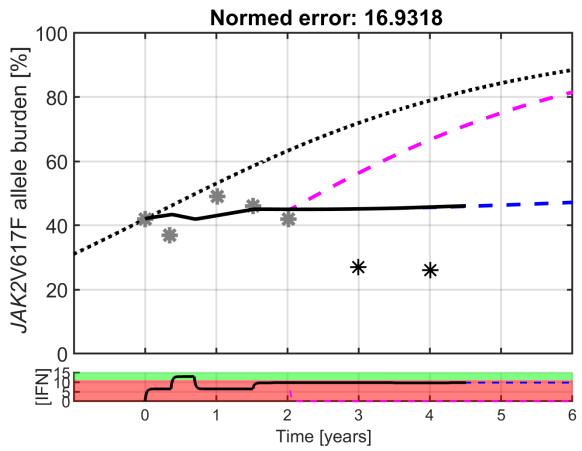
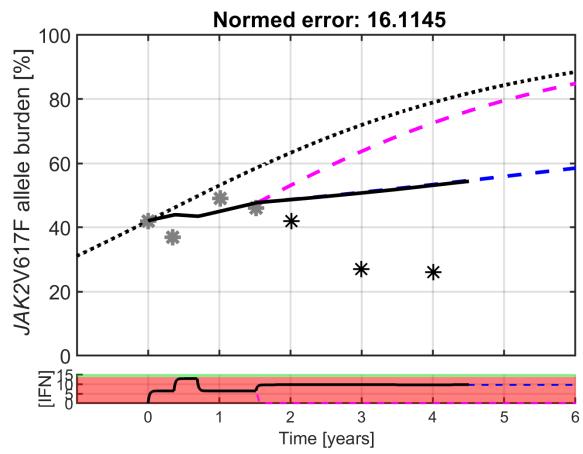
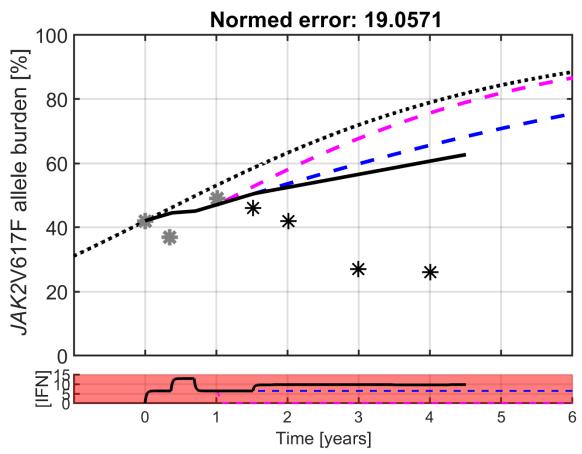


**Patient P028**

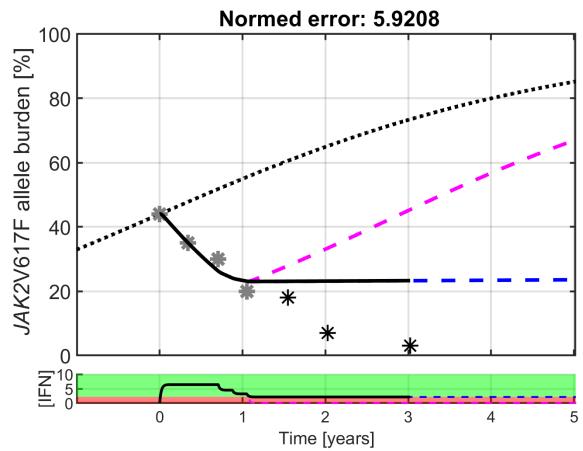
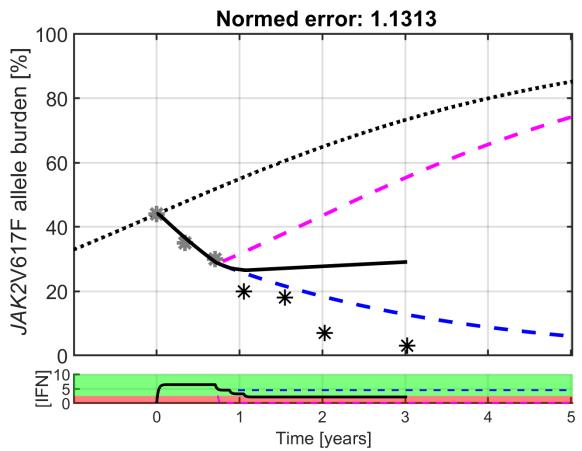


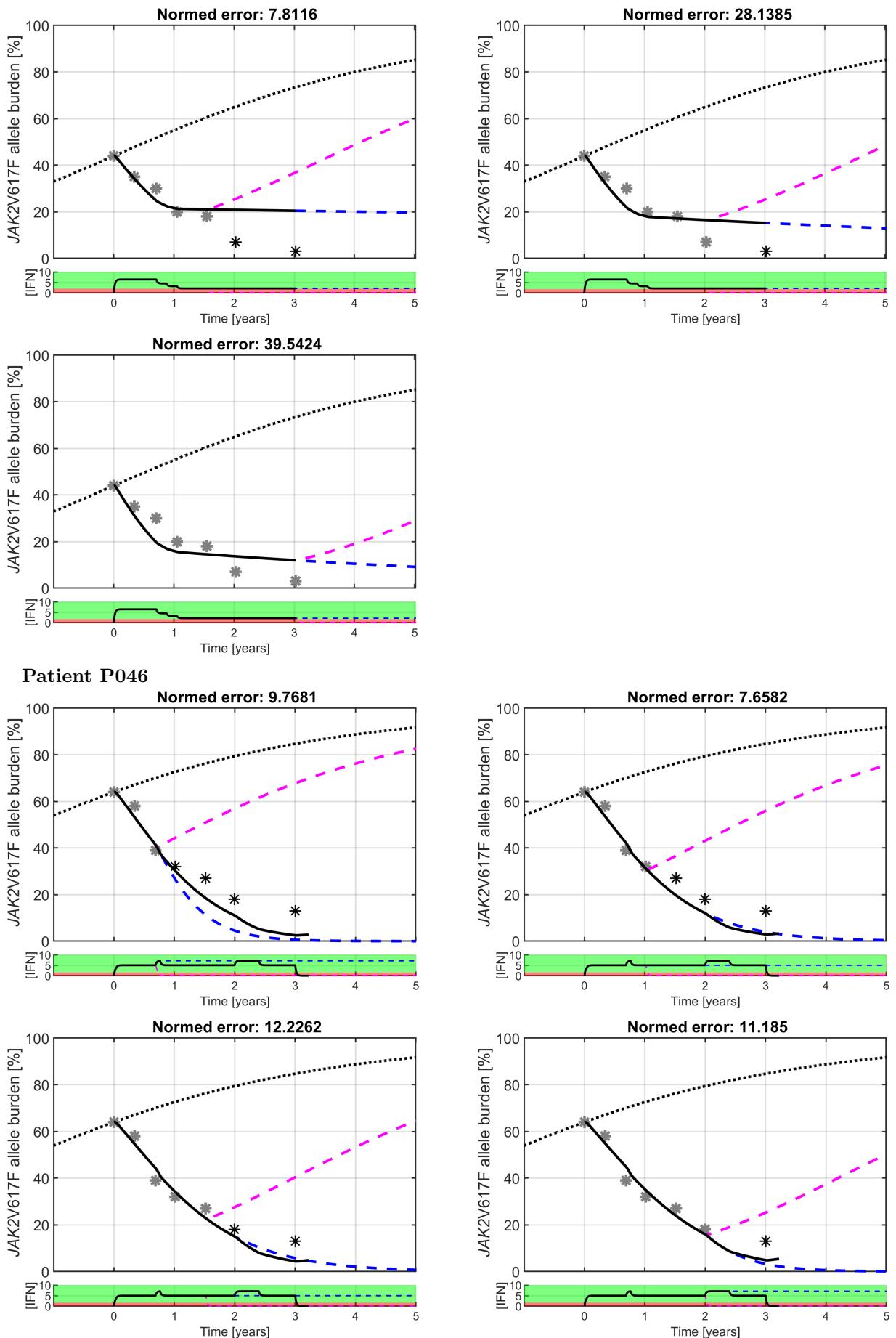


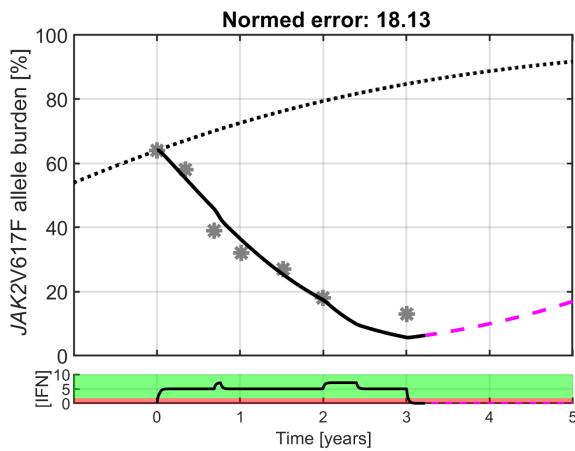




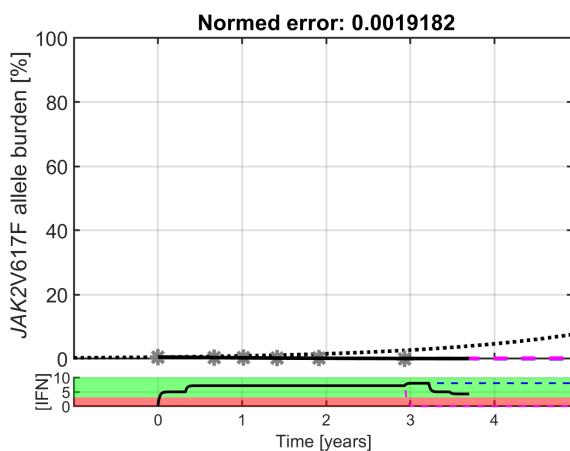
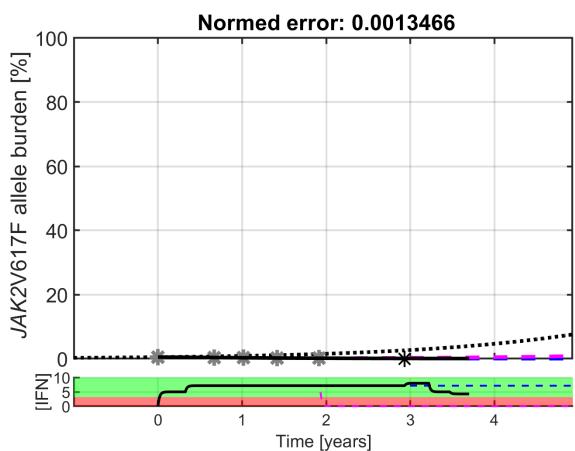
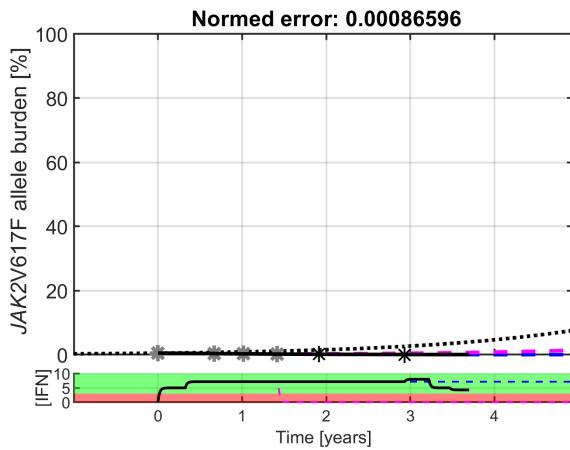
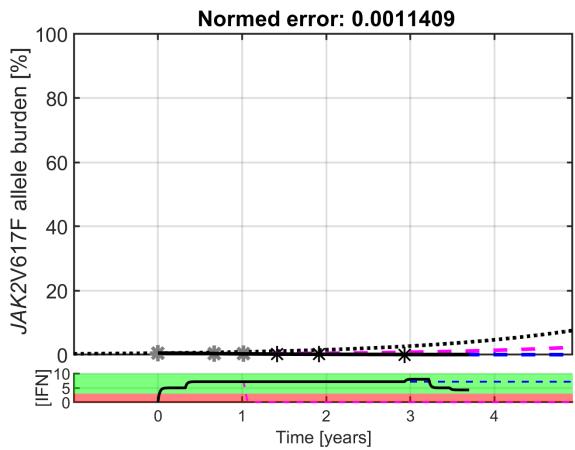
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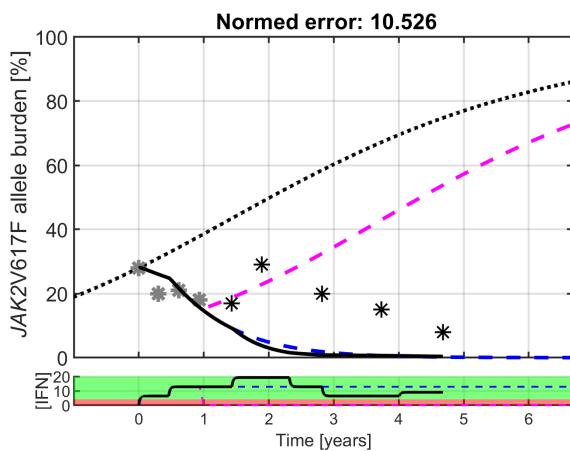
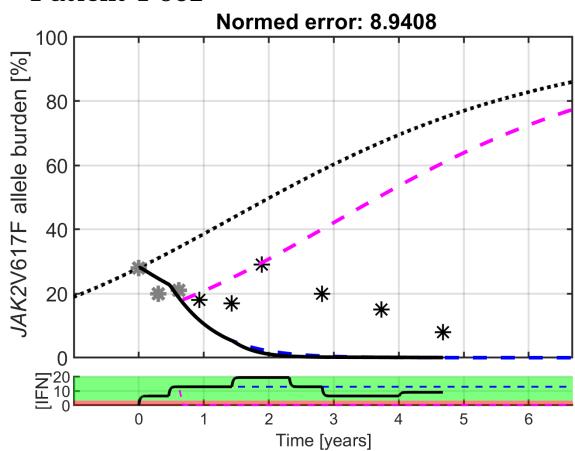


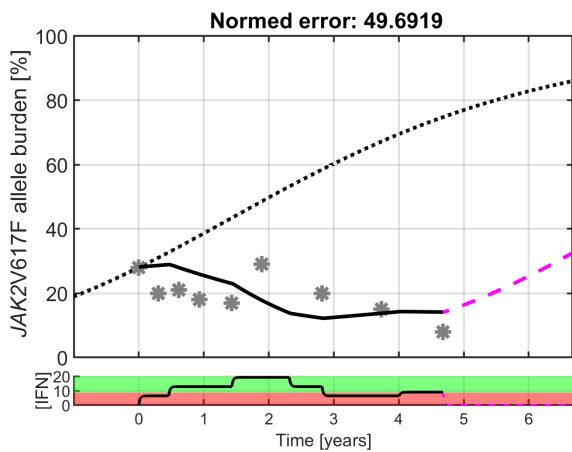
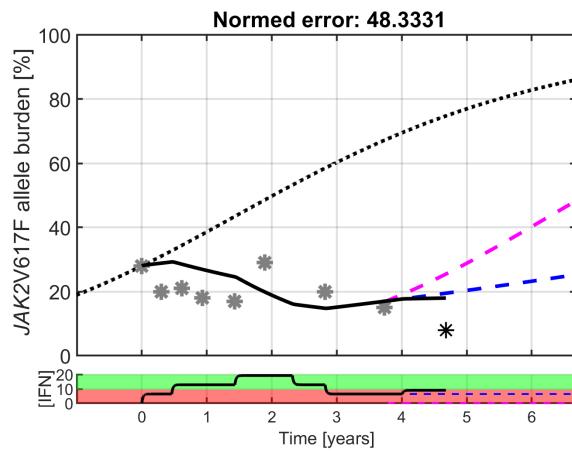
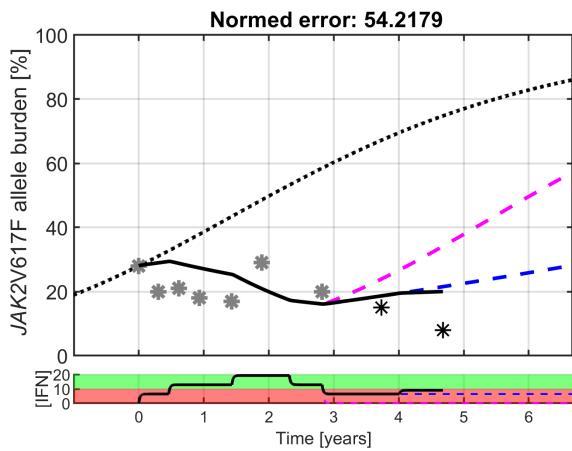
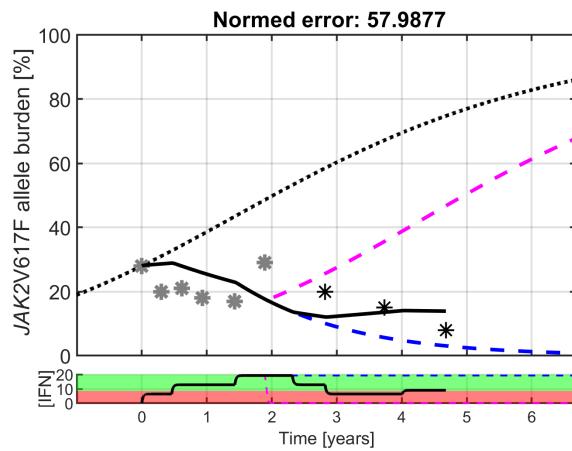
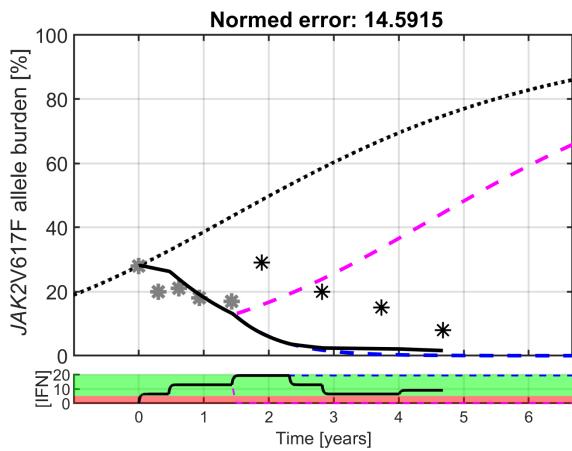


Patient P046

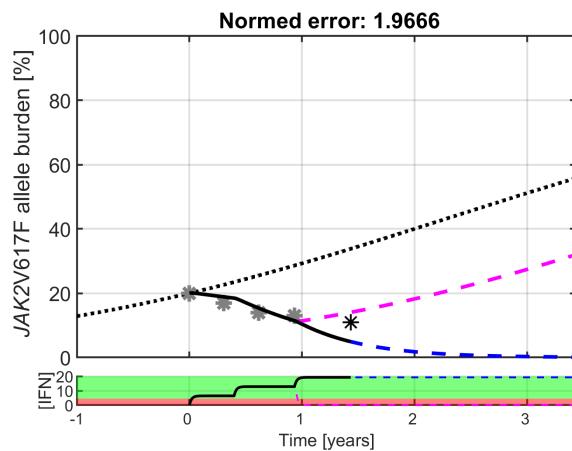
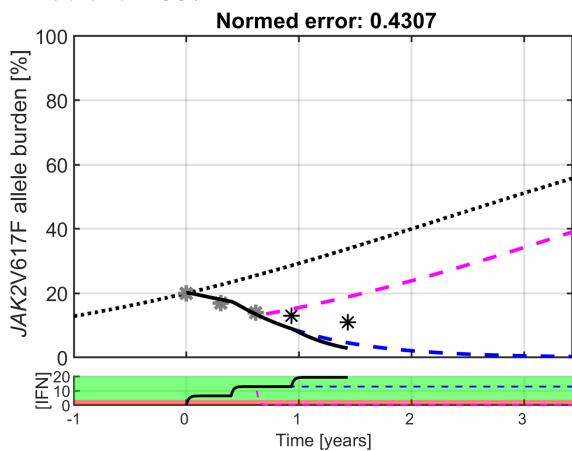


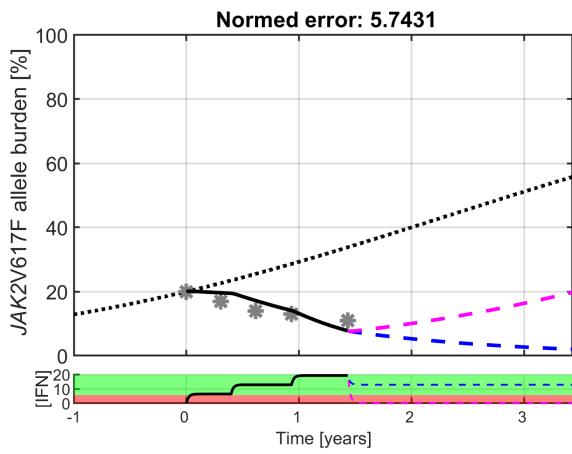
Patient P062



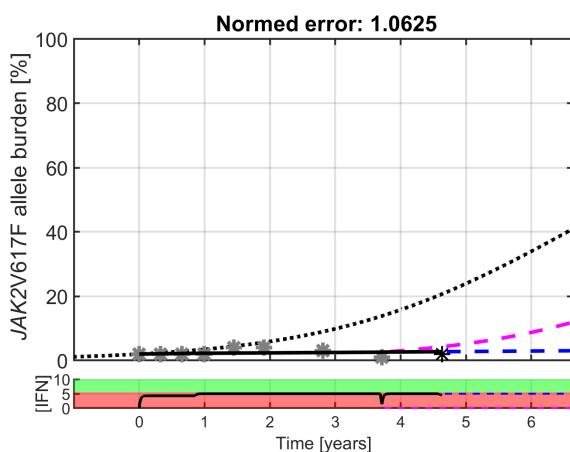
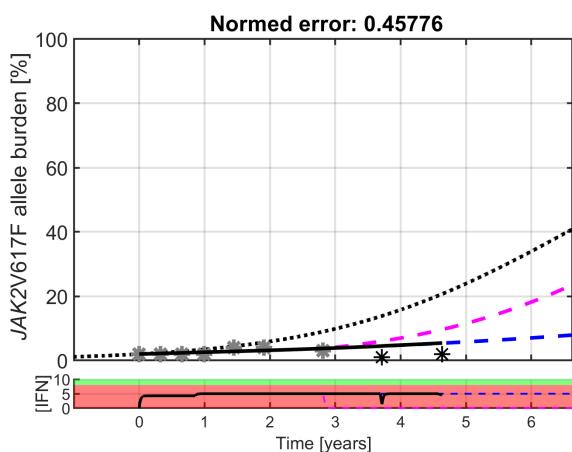
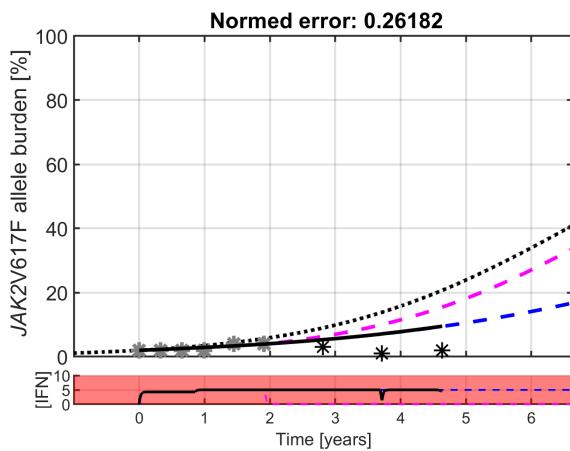
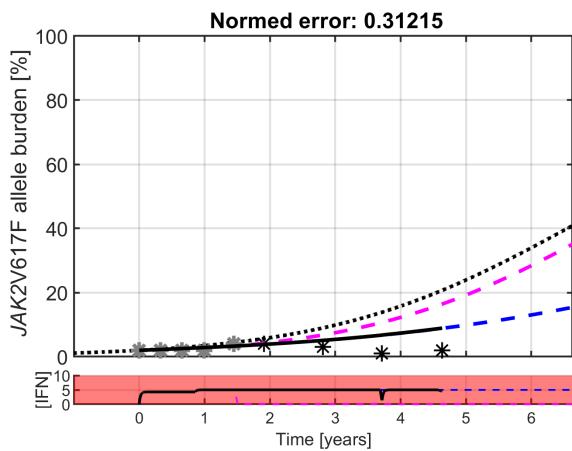
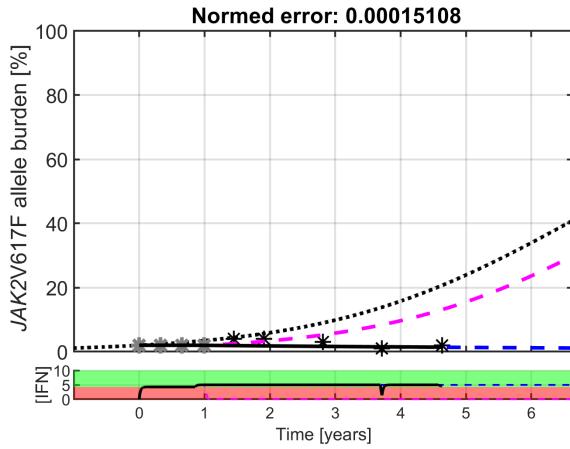
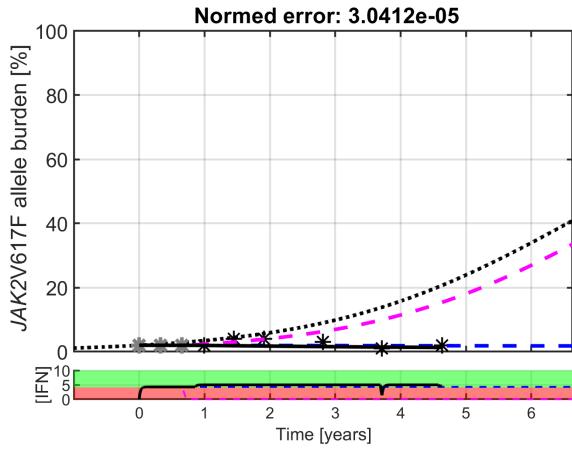


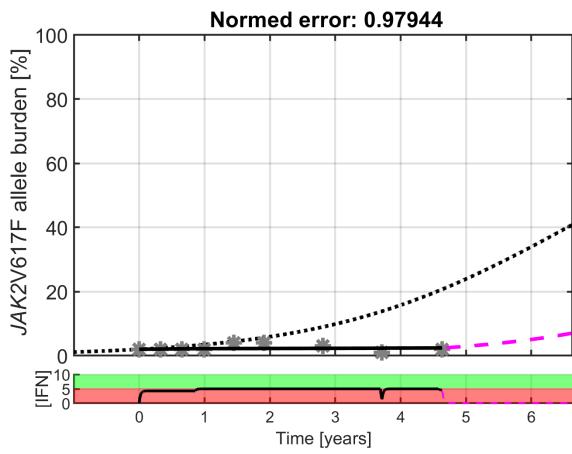
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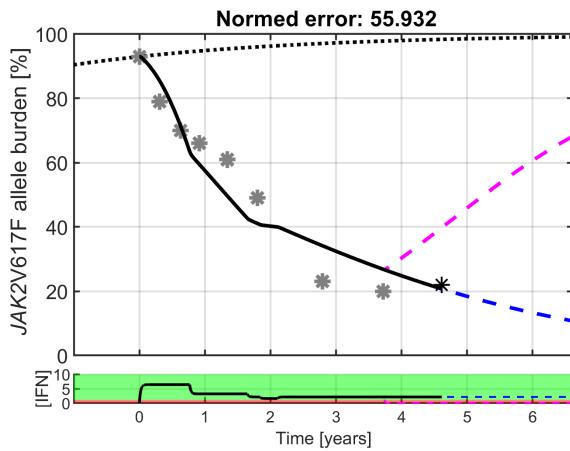
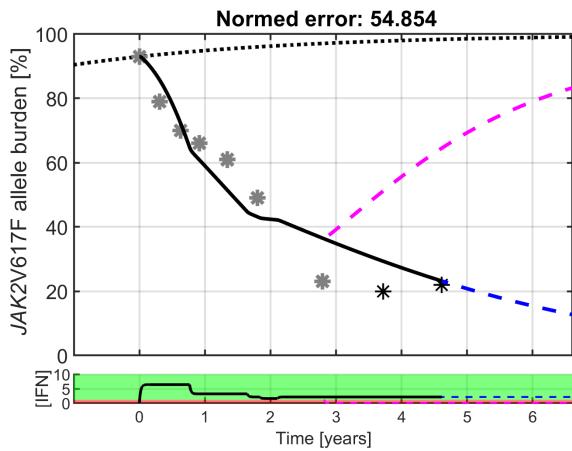
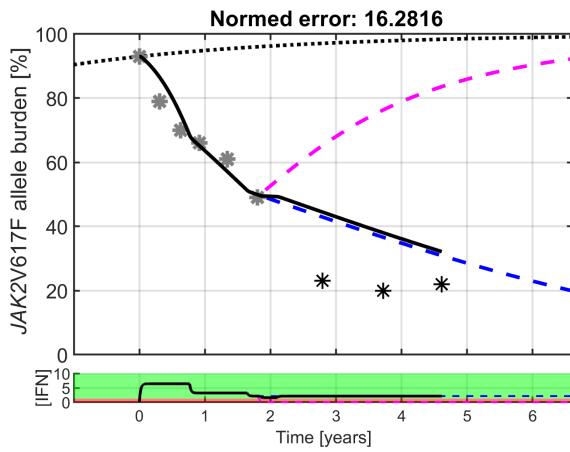
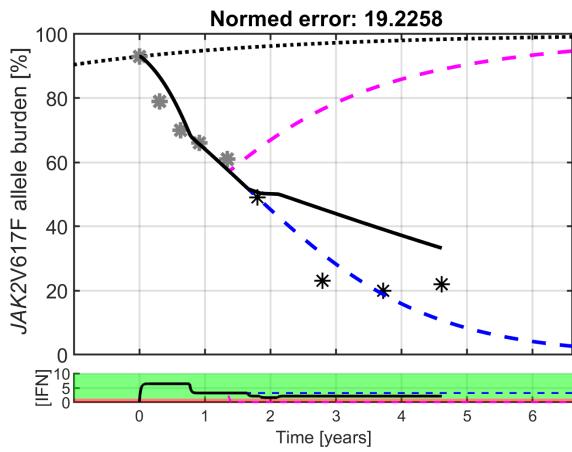
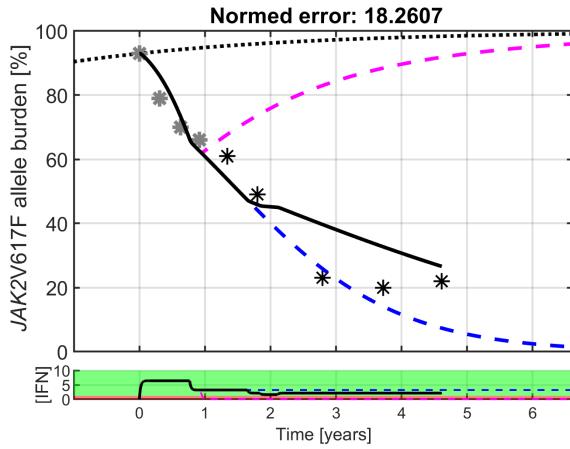
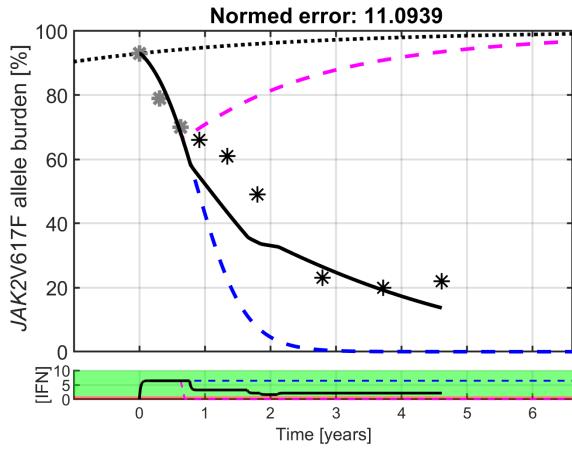


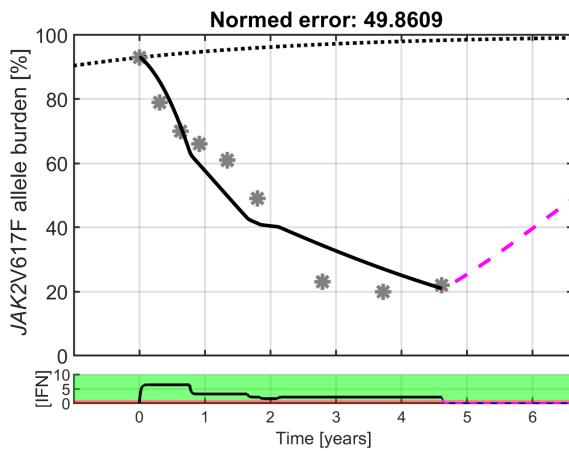
Patient P070



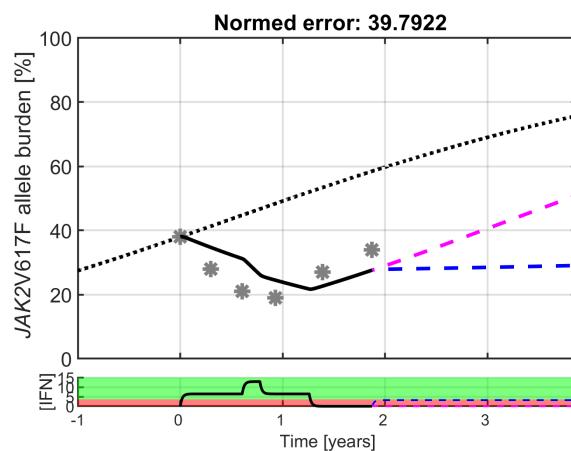
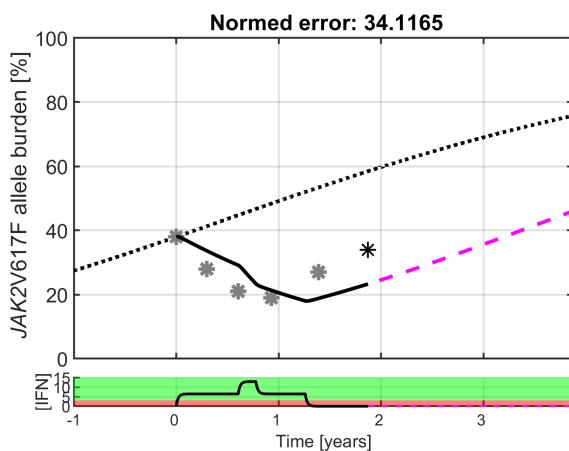
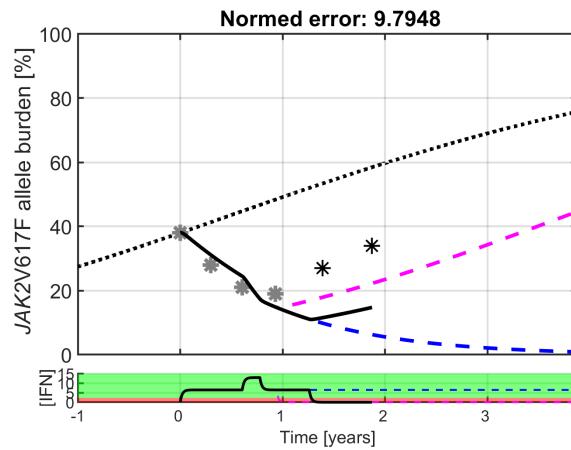
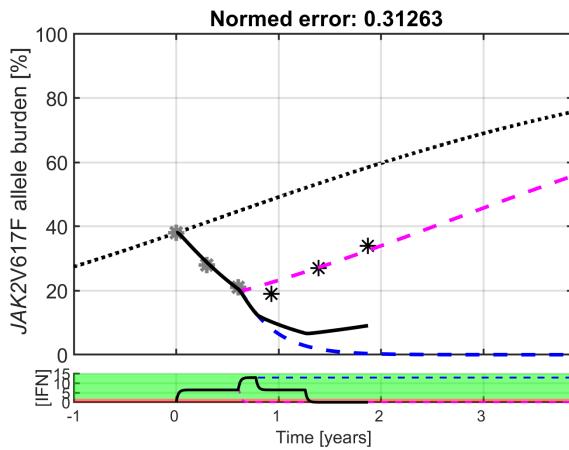


Patient P075

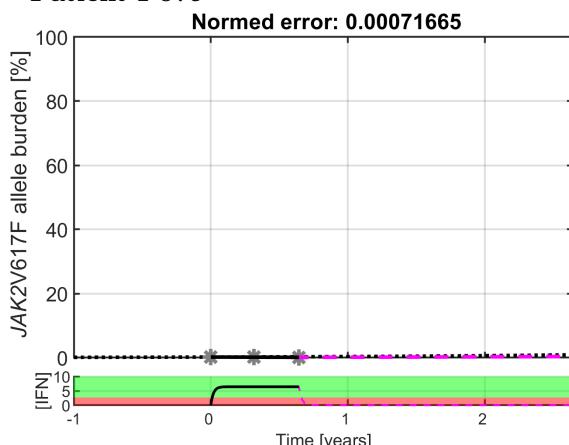




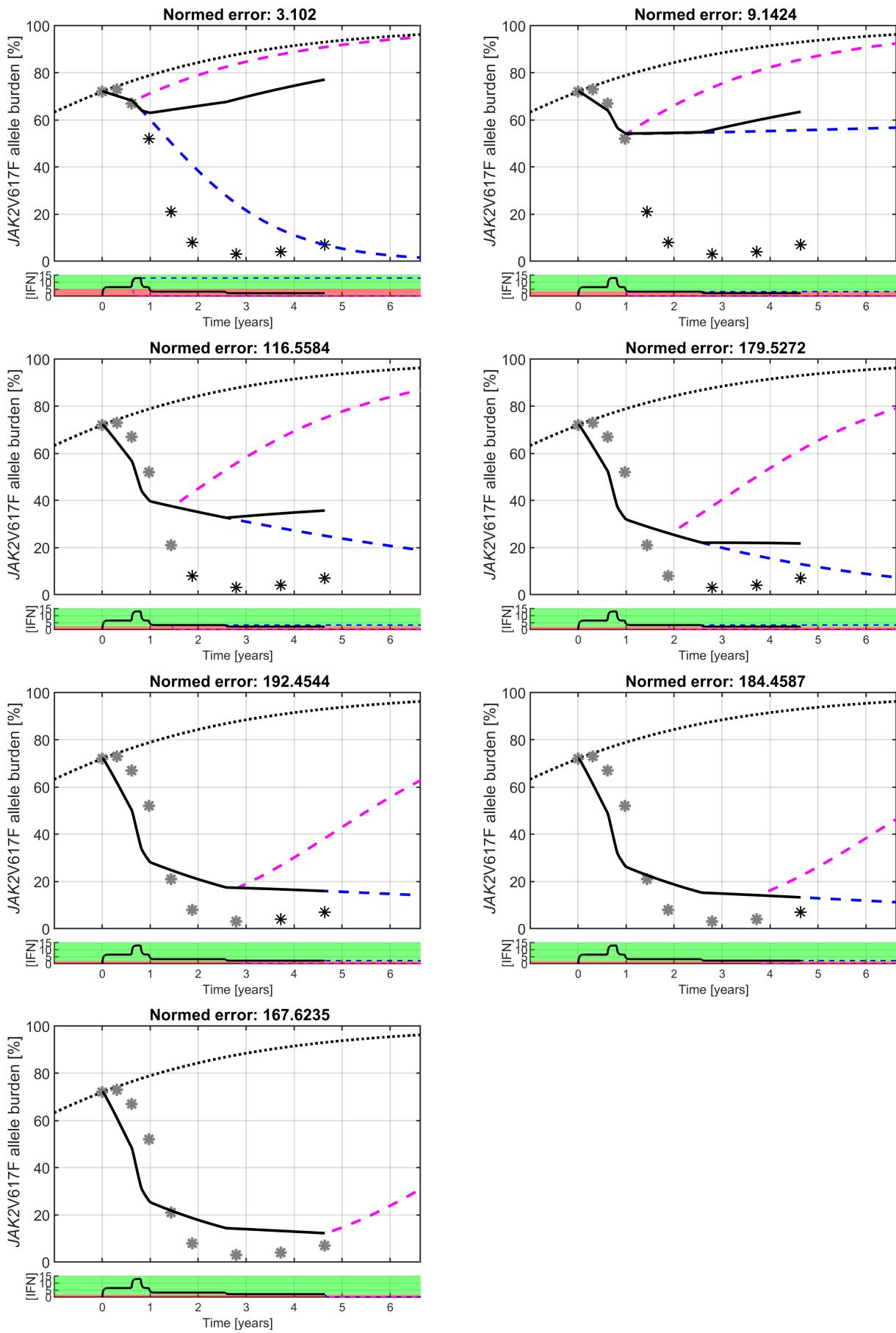
Patient P078

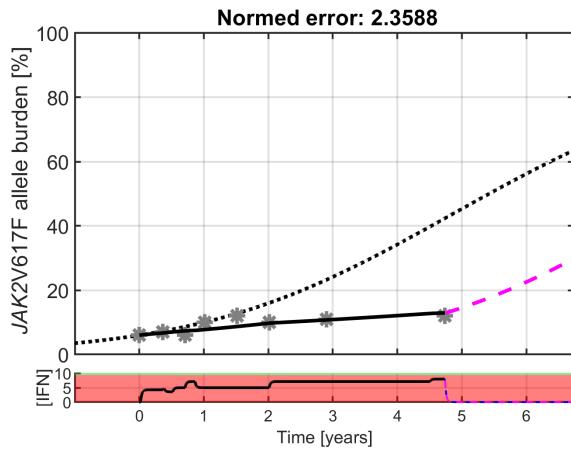
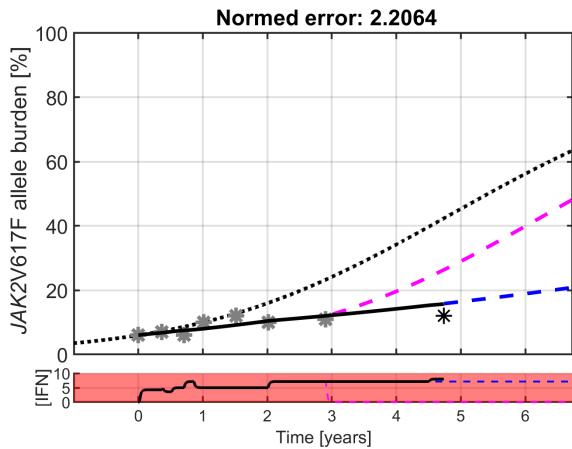
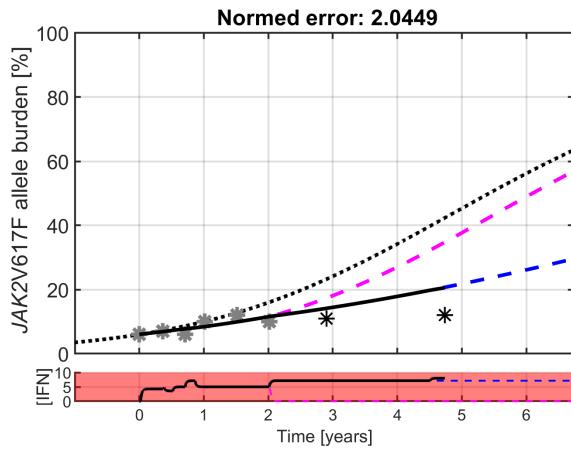
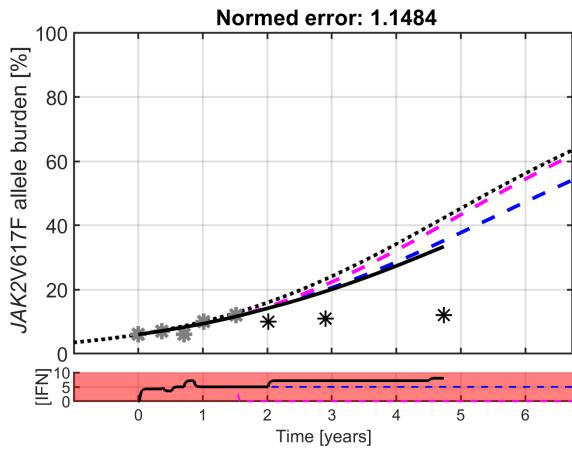
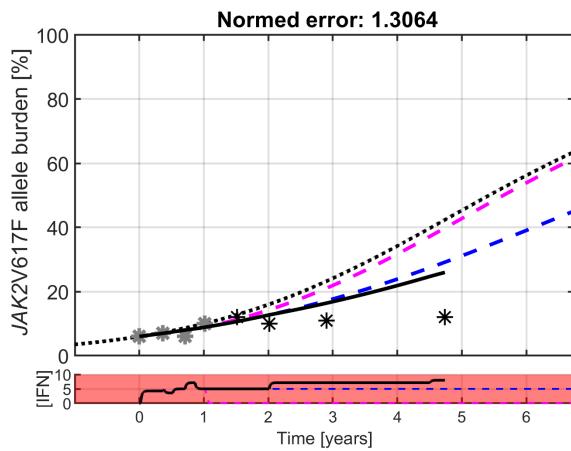
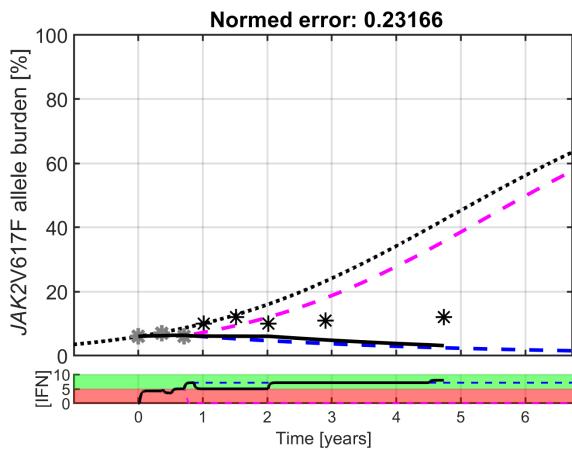


Patient P079

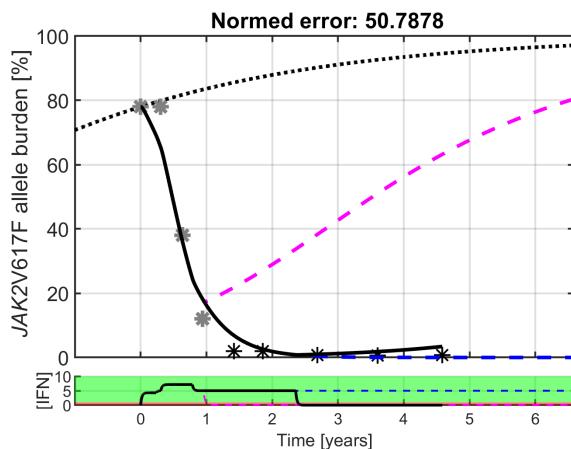
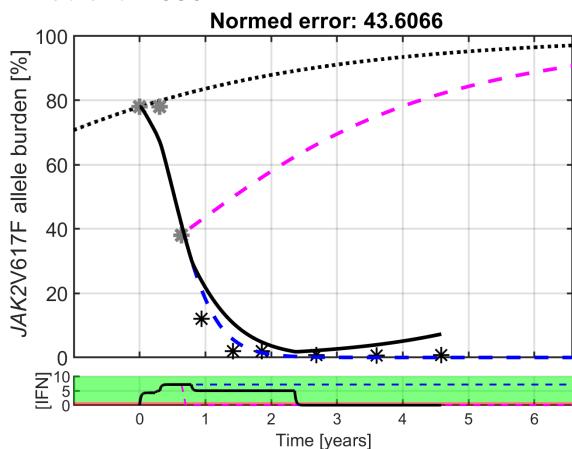


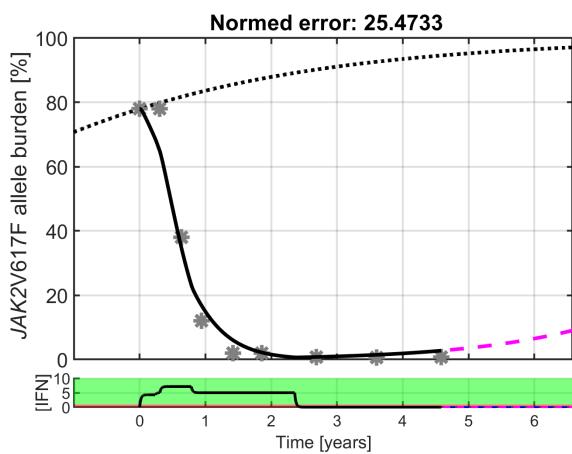
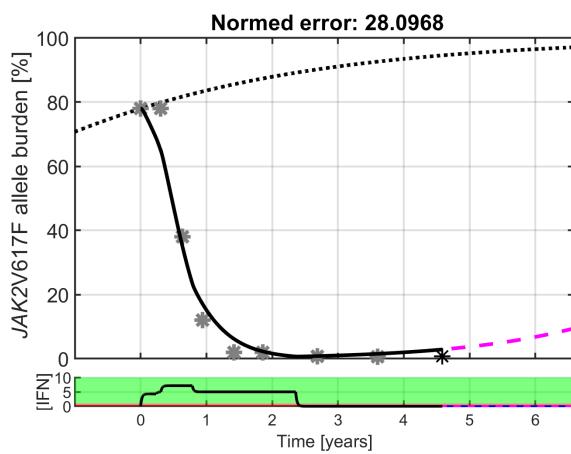
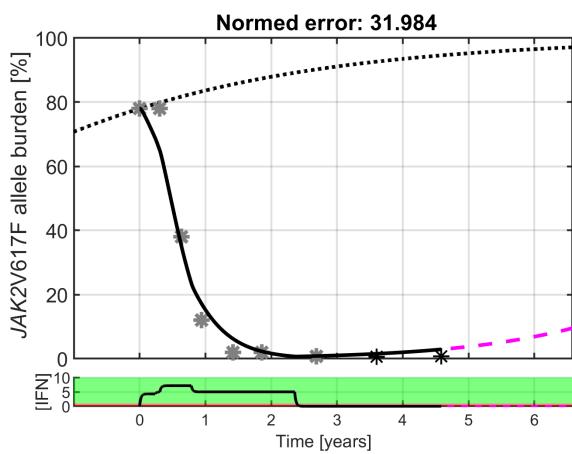
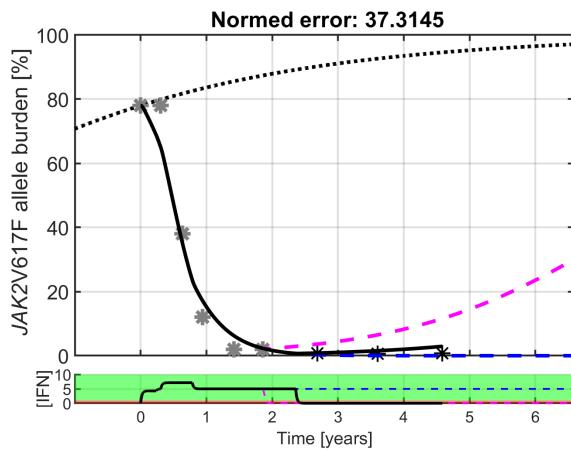
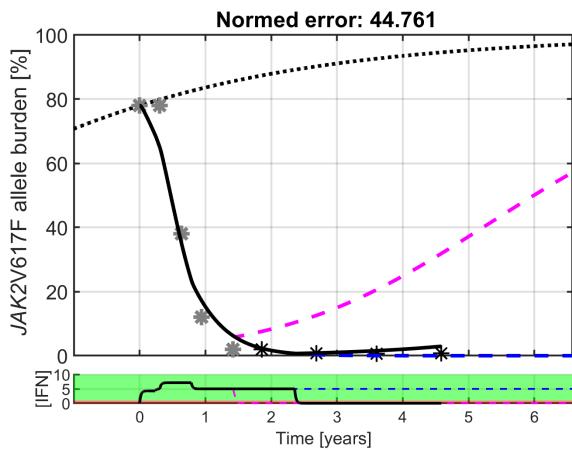
Patient P082



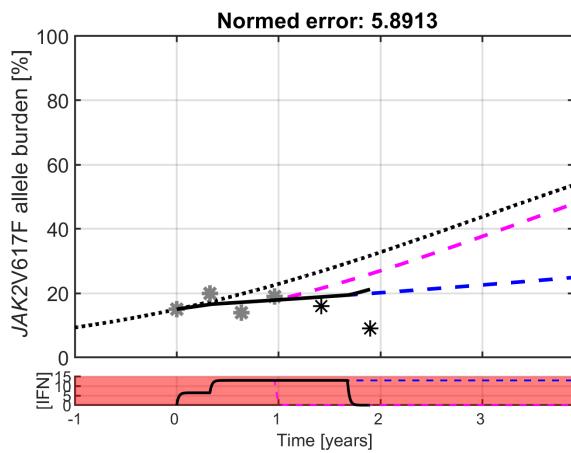
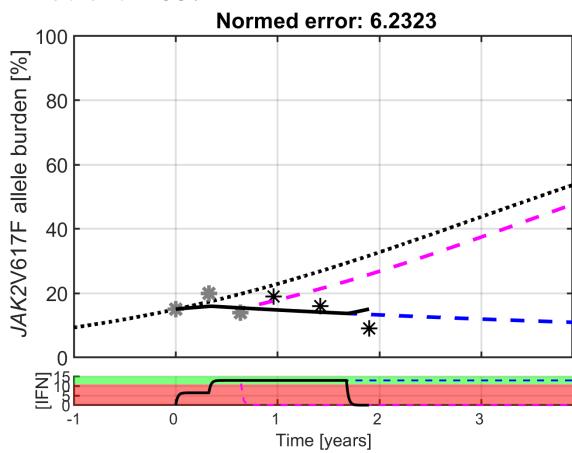


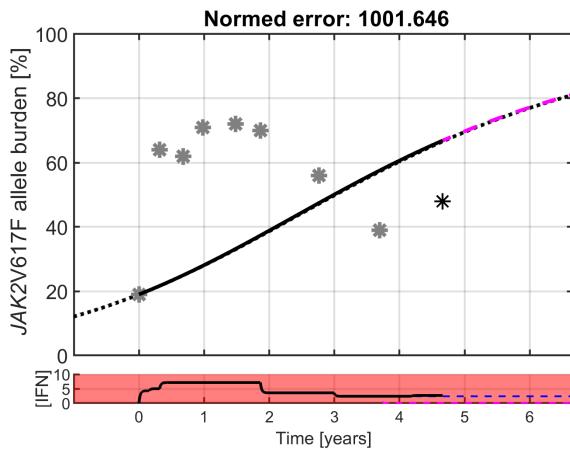
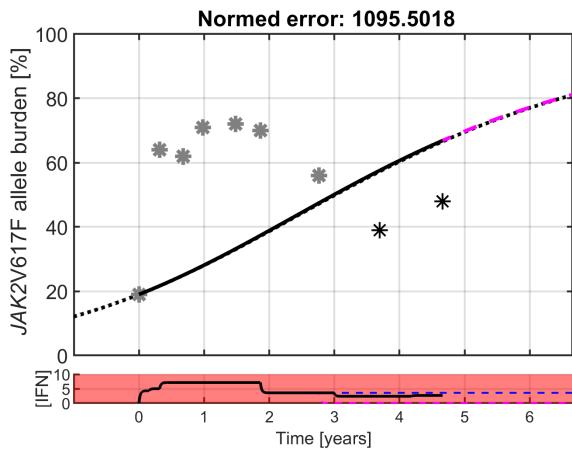
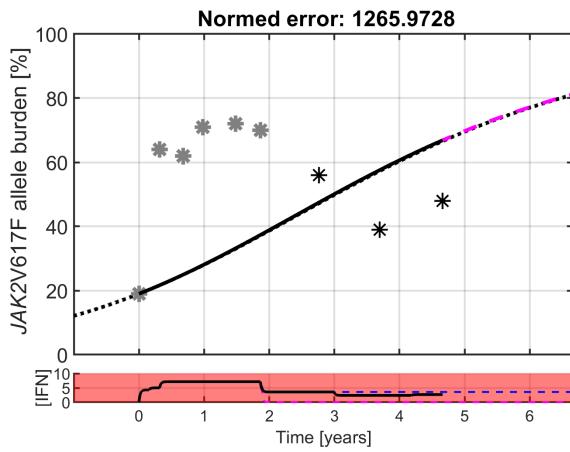
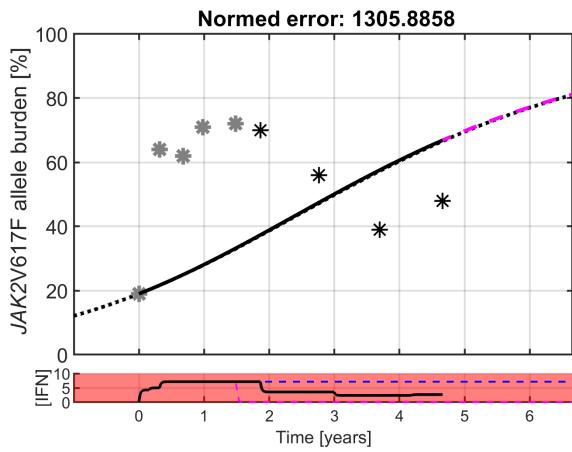
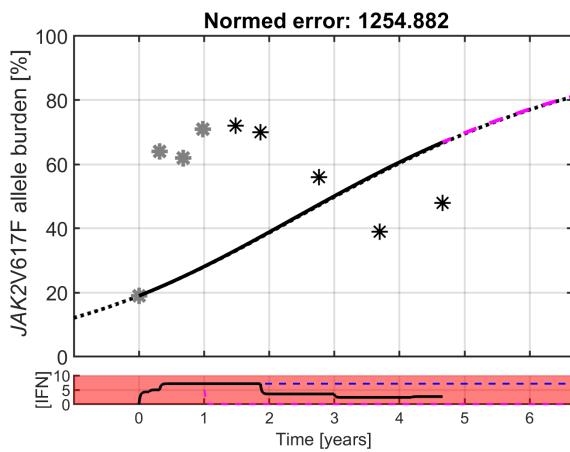
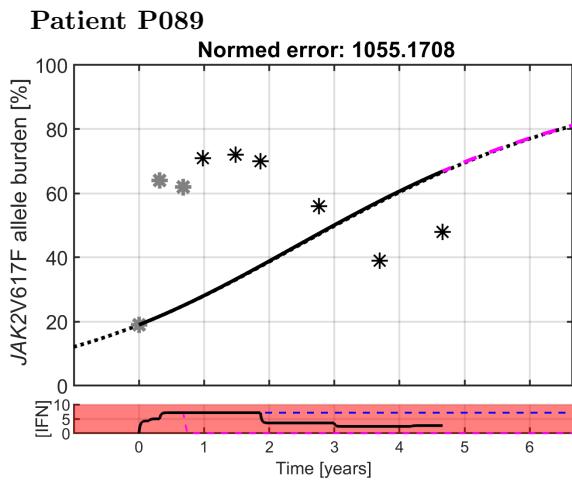
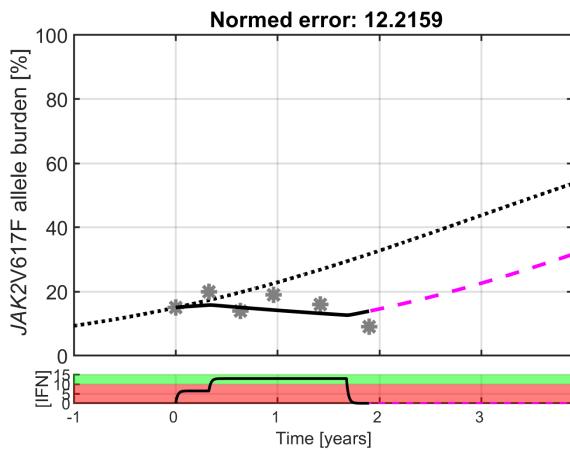
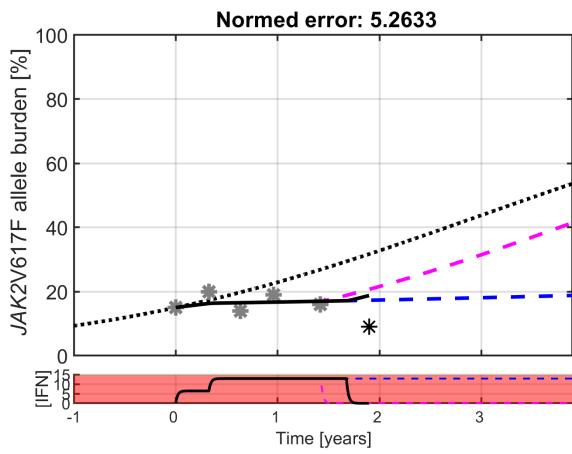
### Patient P086

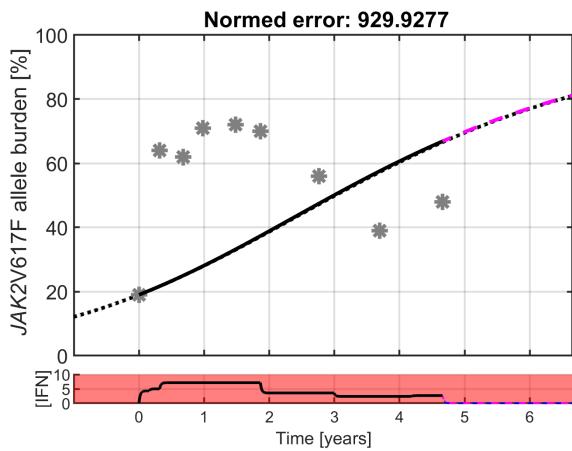




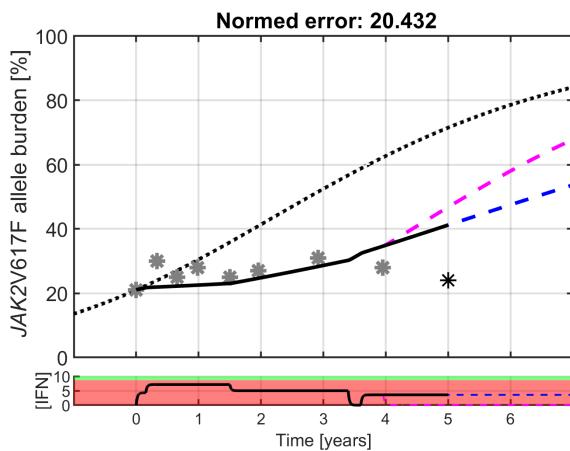
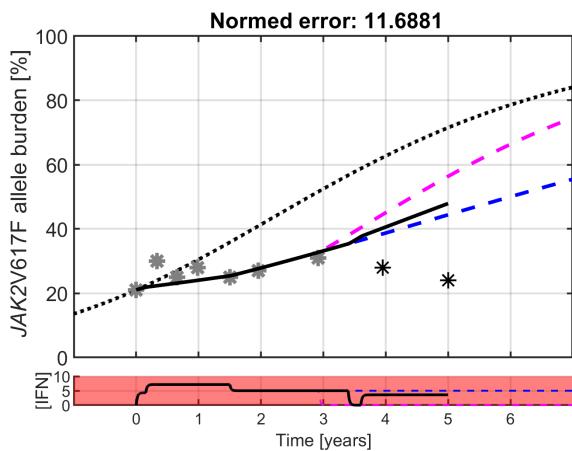
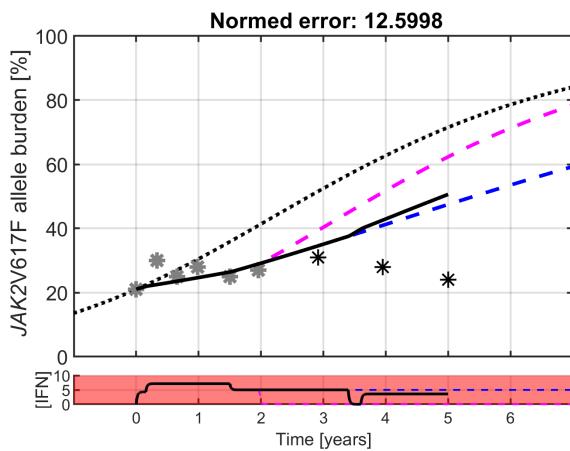
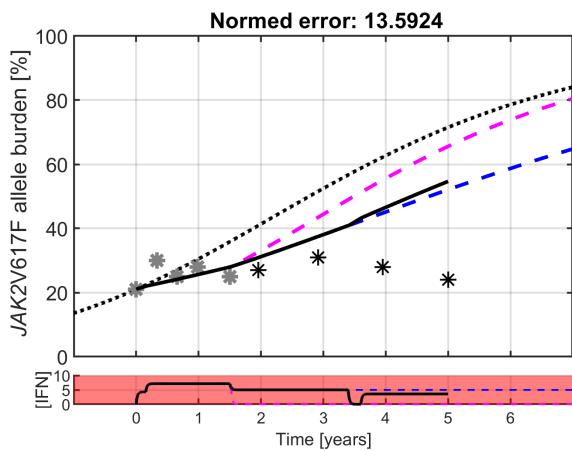
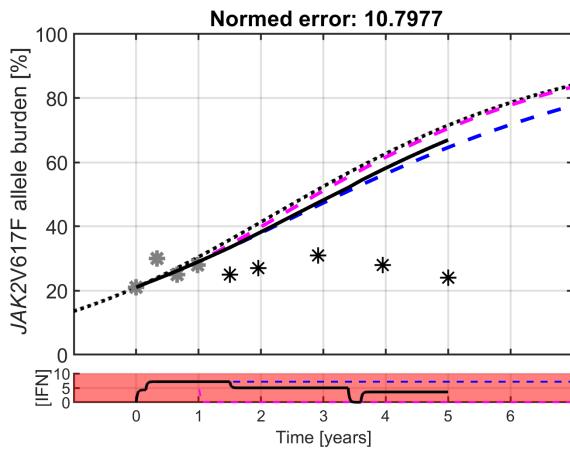
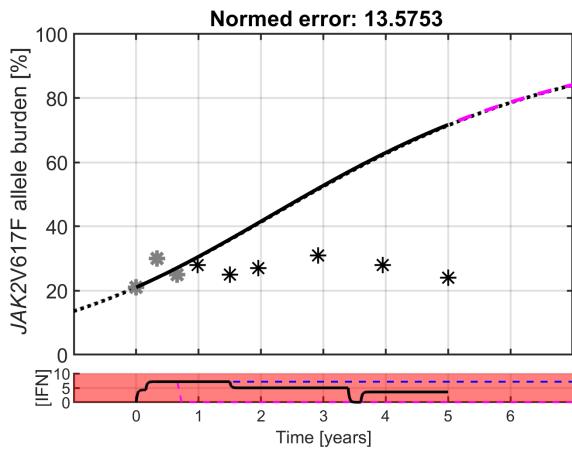
### Patient P087

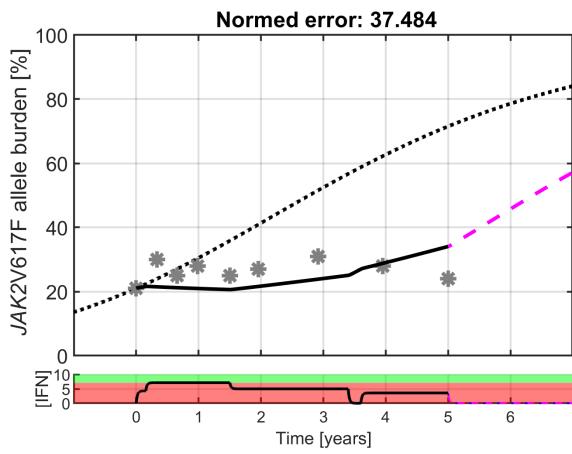




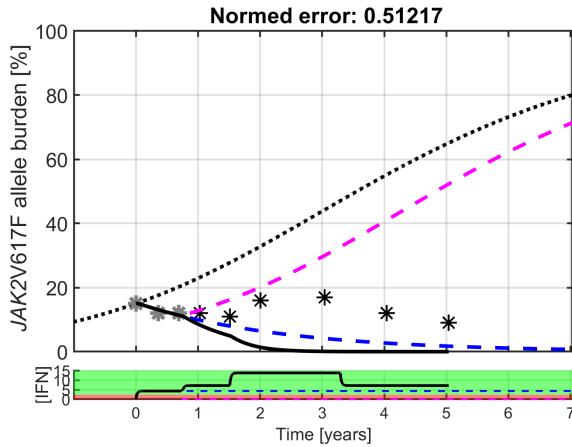


Patient P105

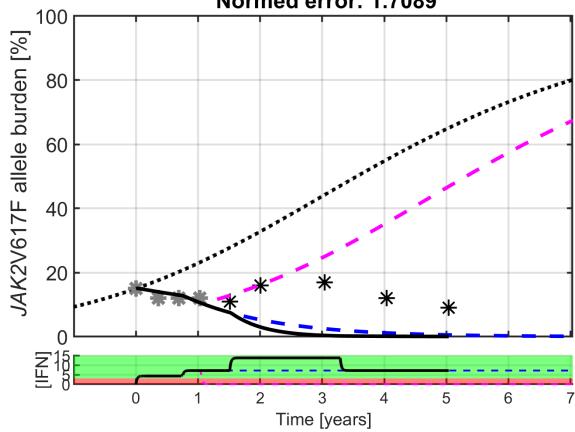




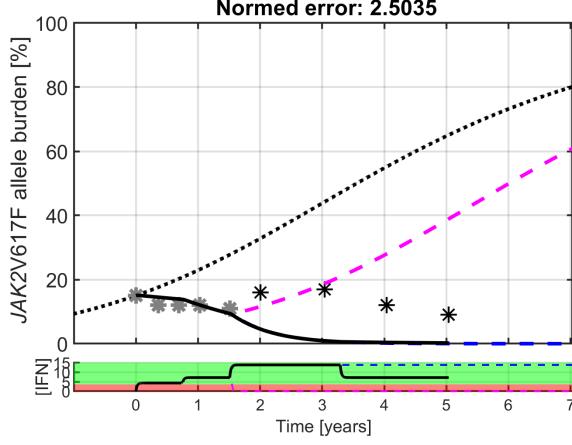
Patient P106



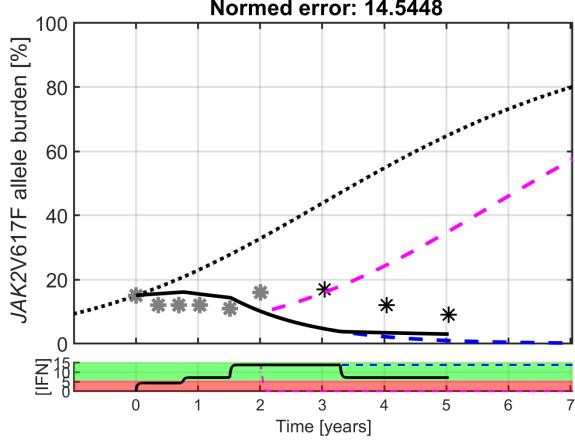
Normed error: 1.7089



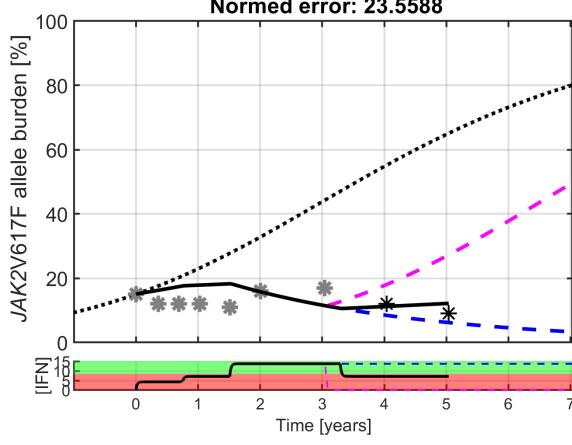
Normed error: 2.5035



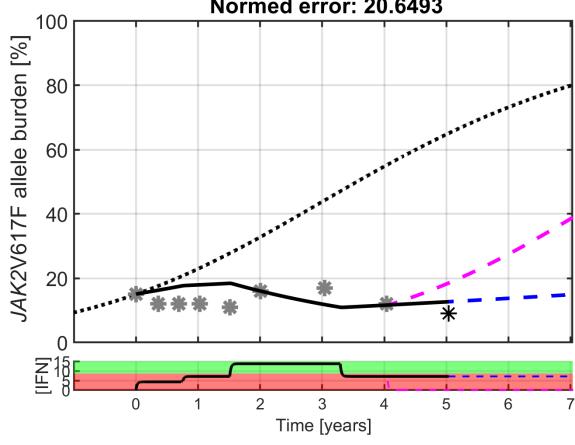
Normed error: 14.5448

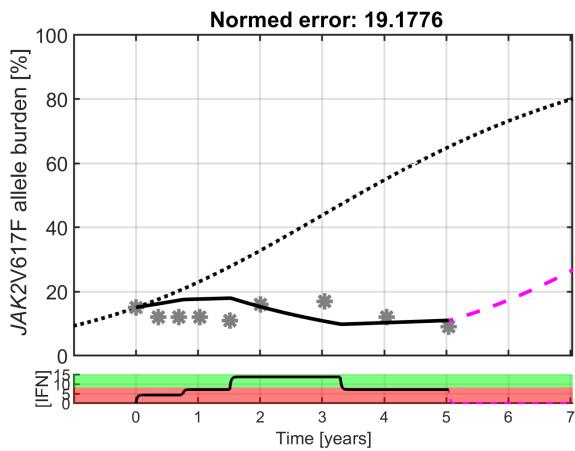


Normed error: 23.5588

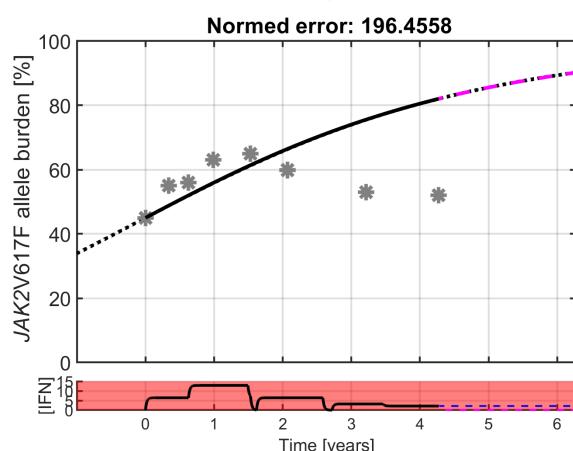
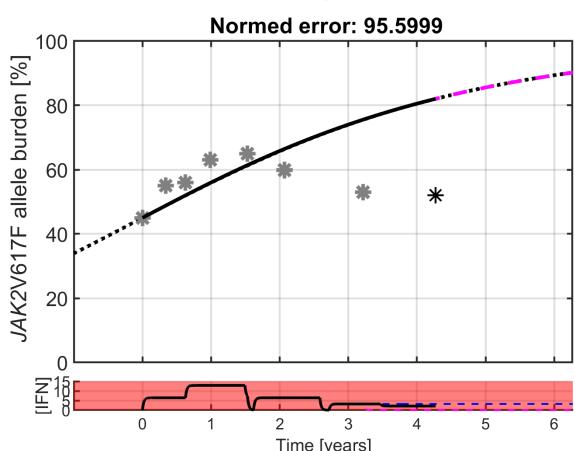
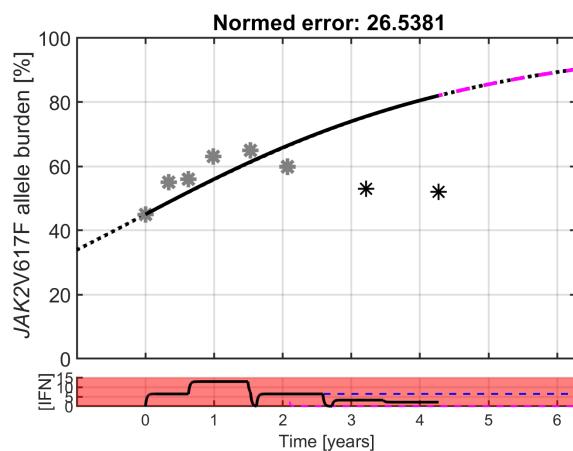
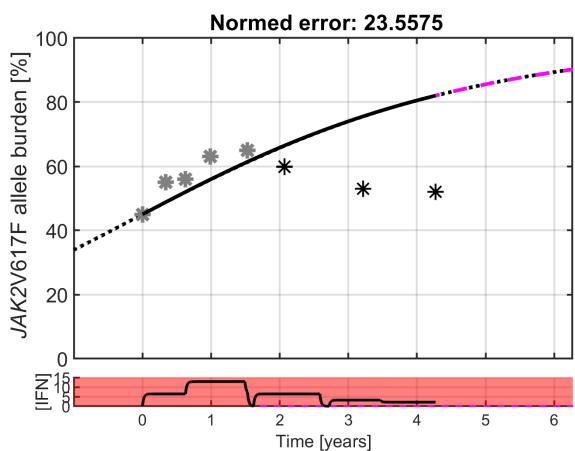
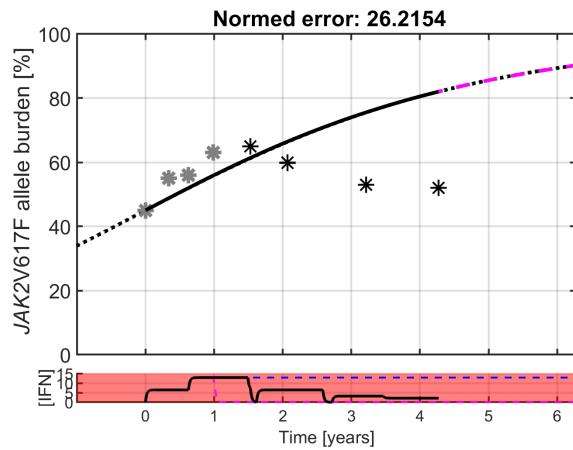
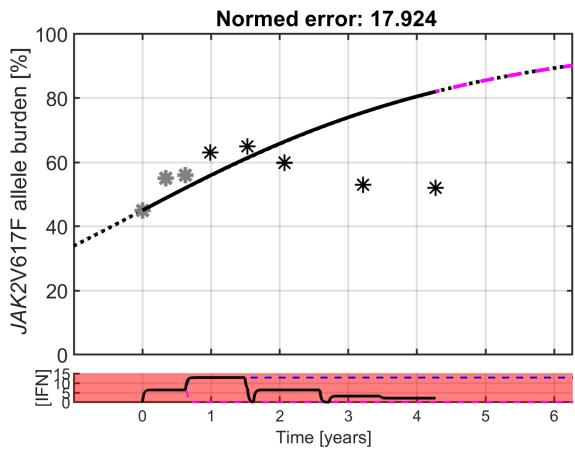


Normed error: 20.6493

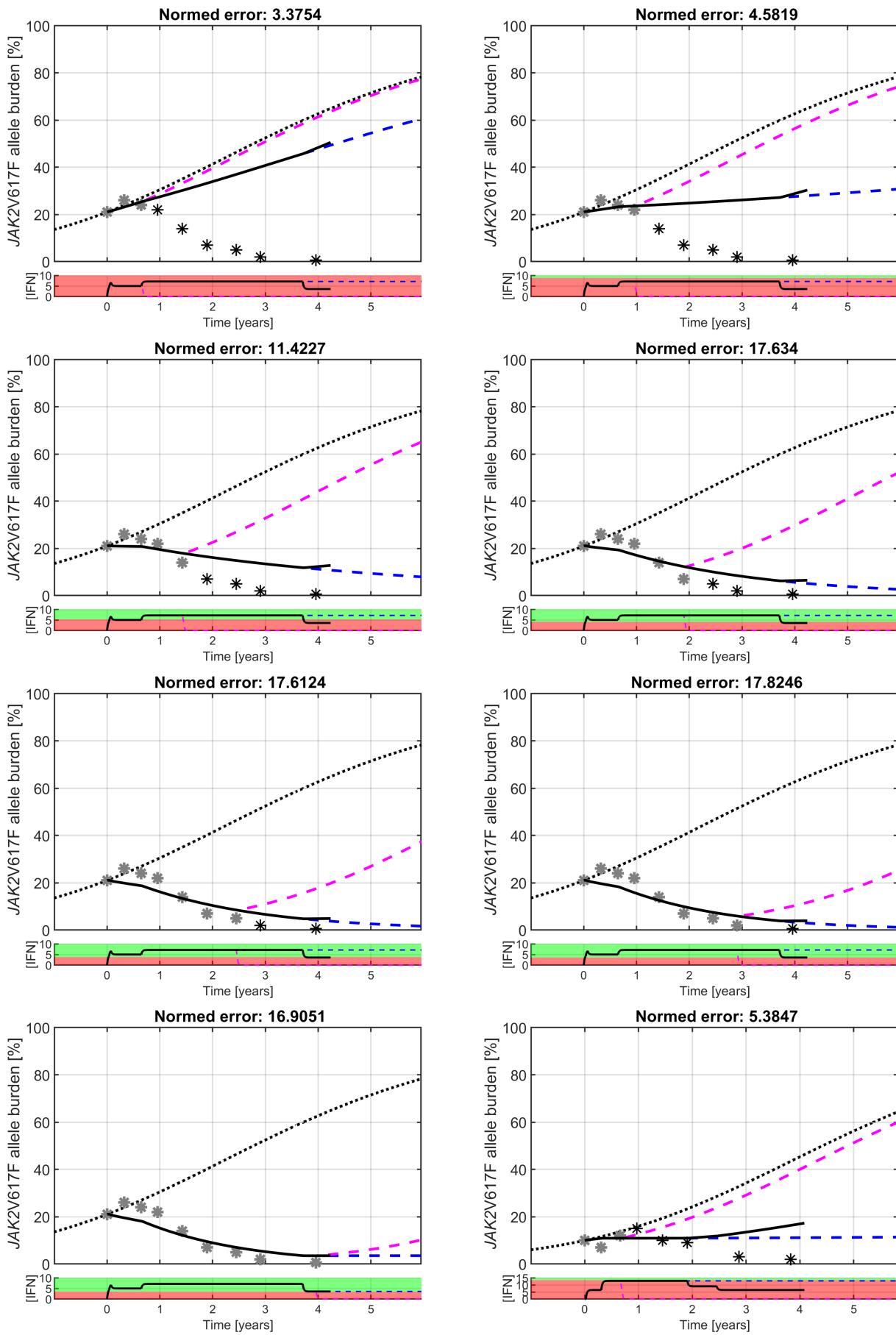




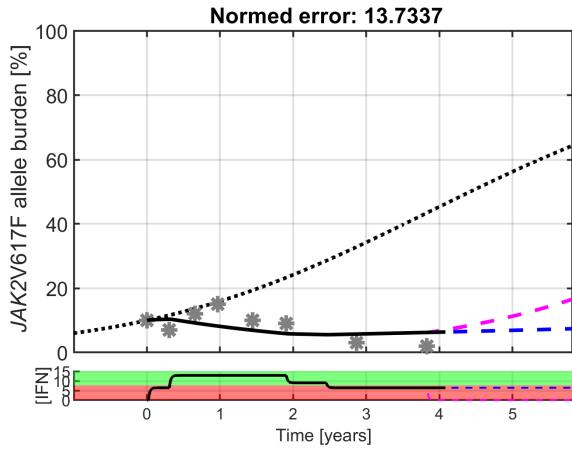
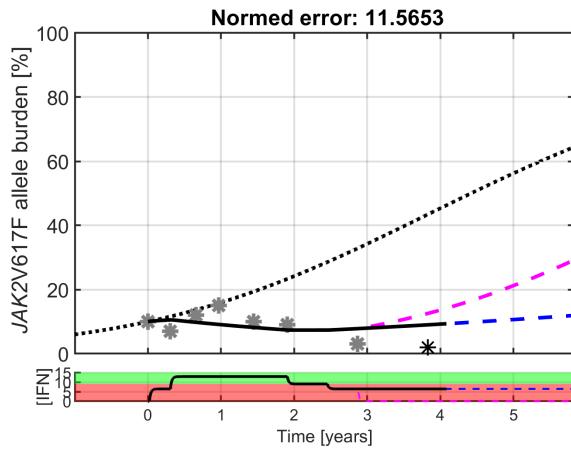
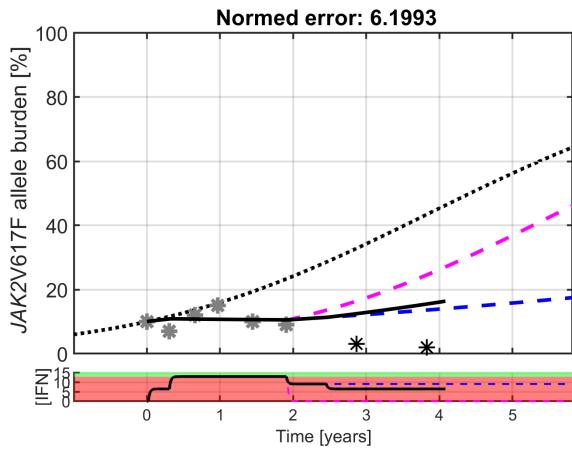
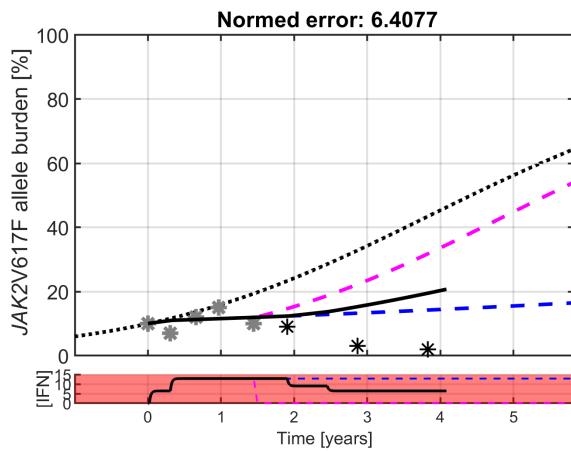
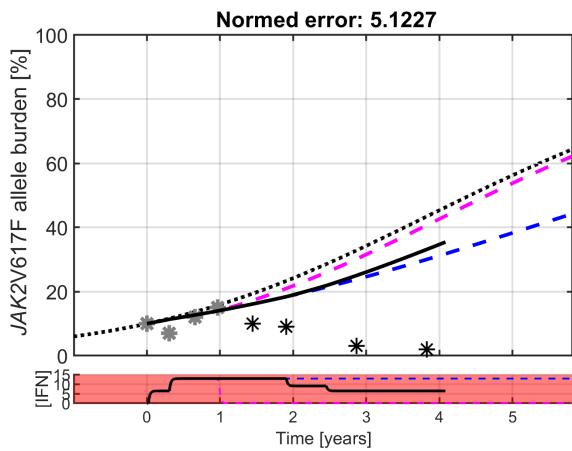
Patient P111



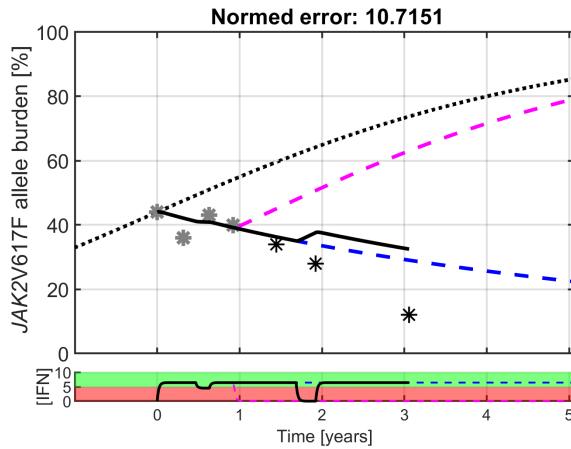
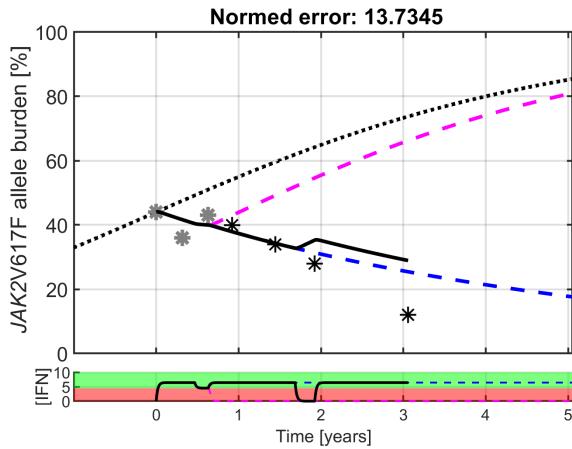
Patient P113

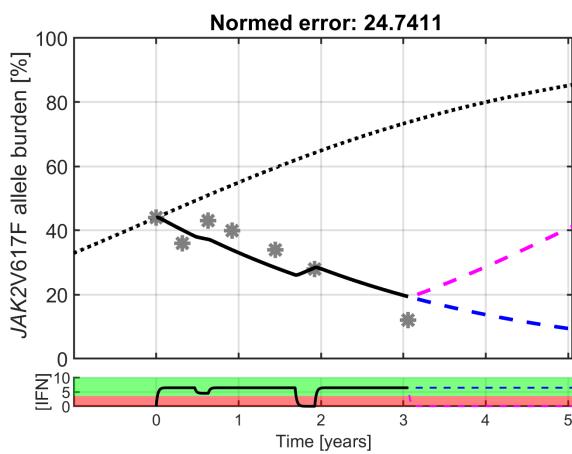
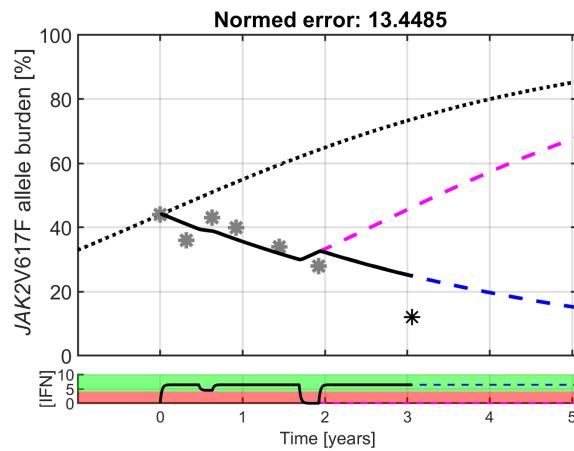
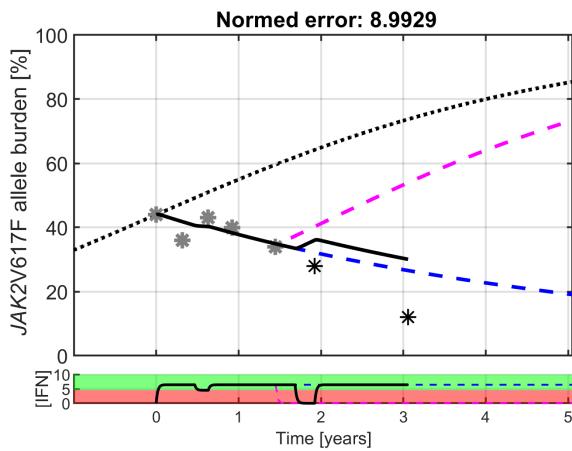


Patient P114

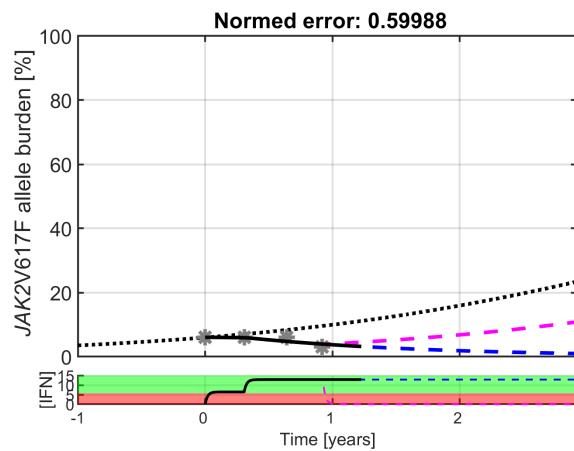
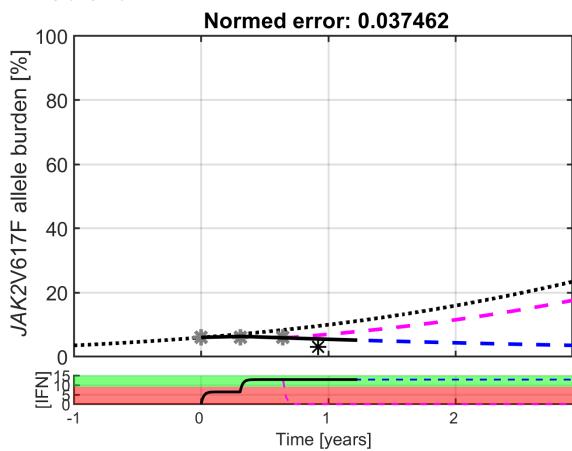


### Patient P117

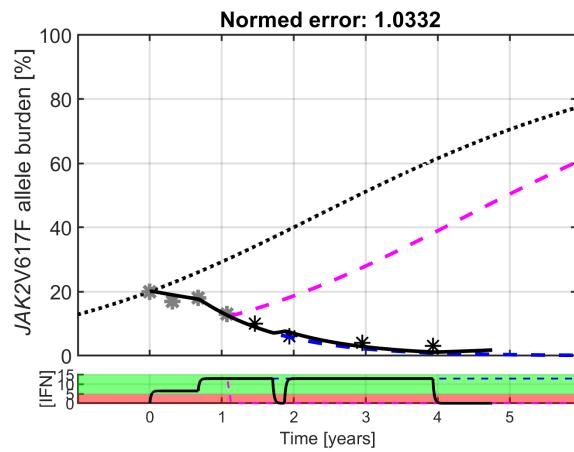
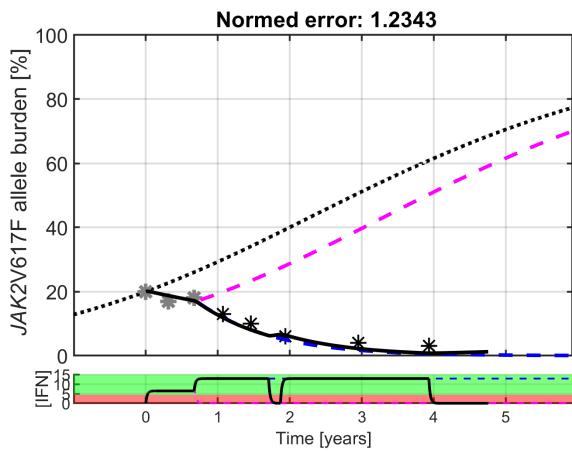


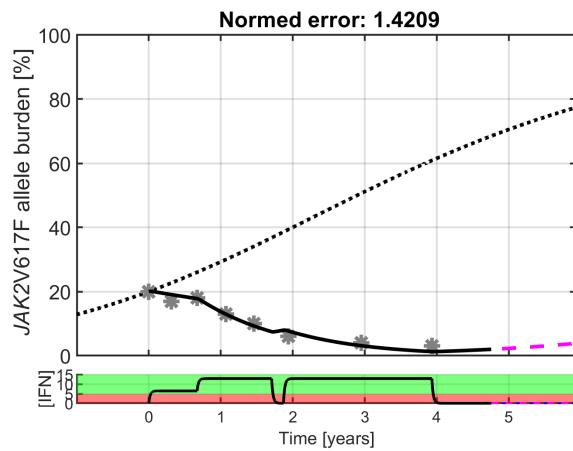
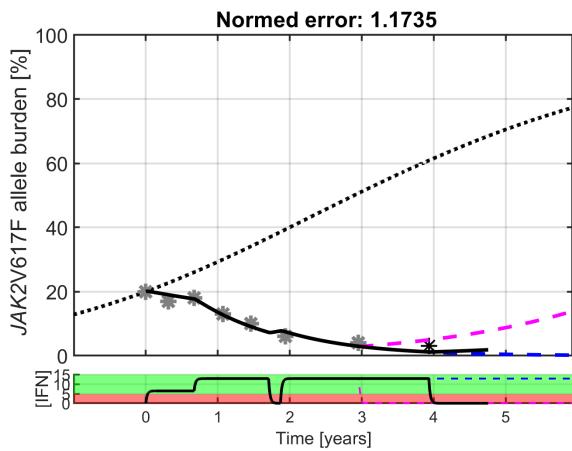
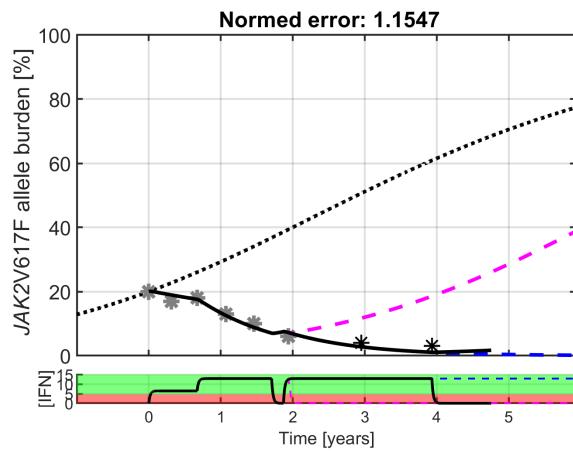
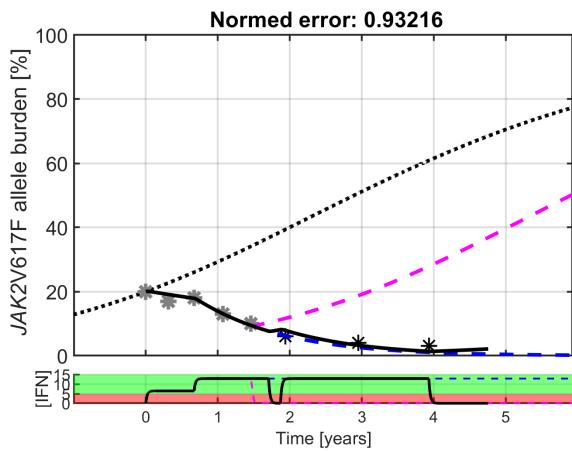


Patient P122

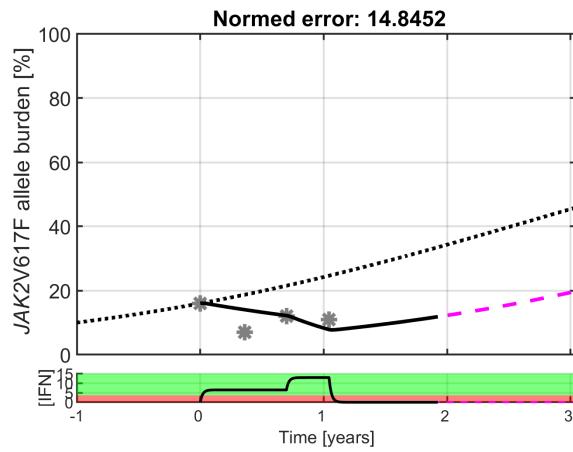
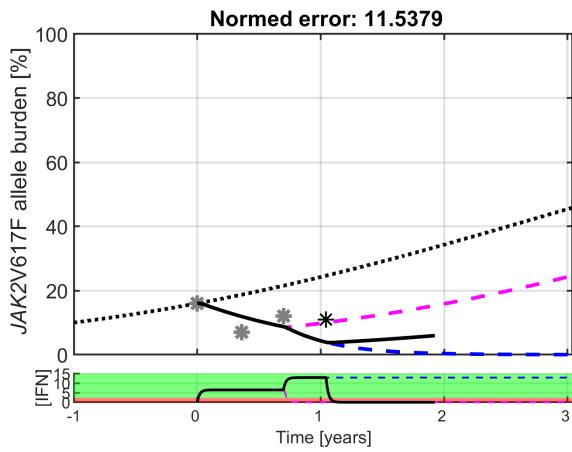


Patient P124

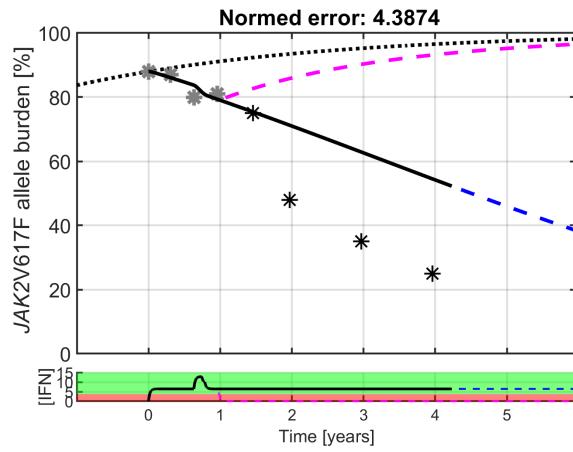
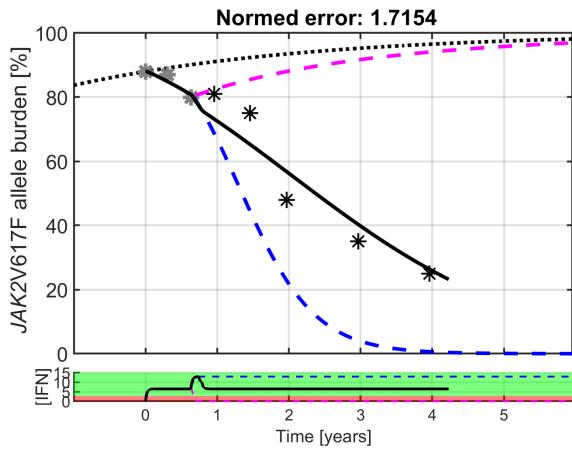


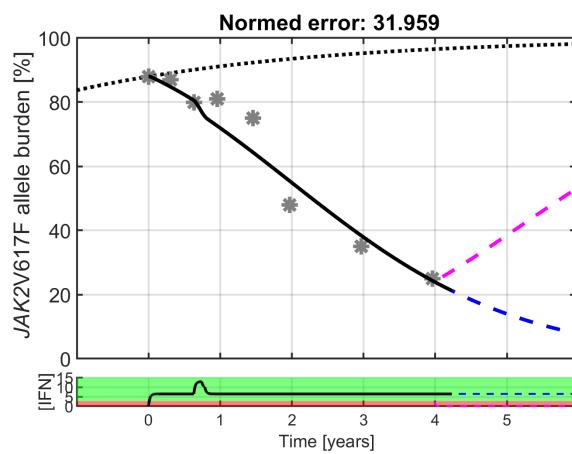
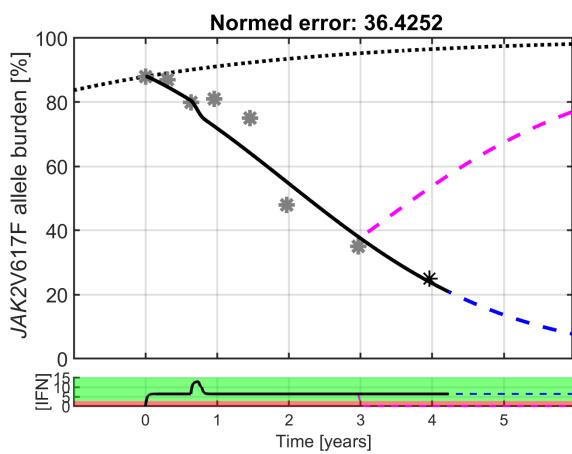
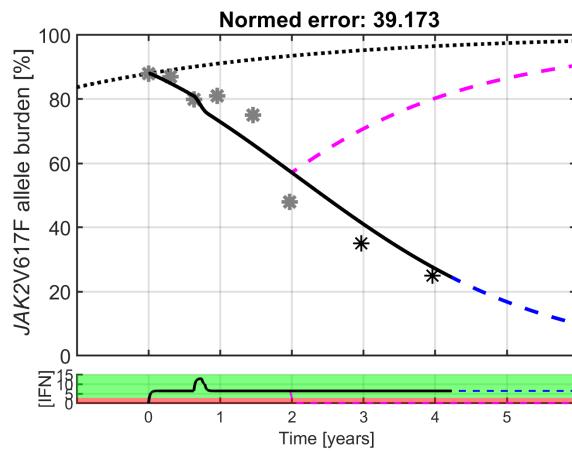
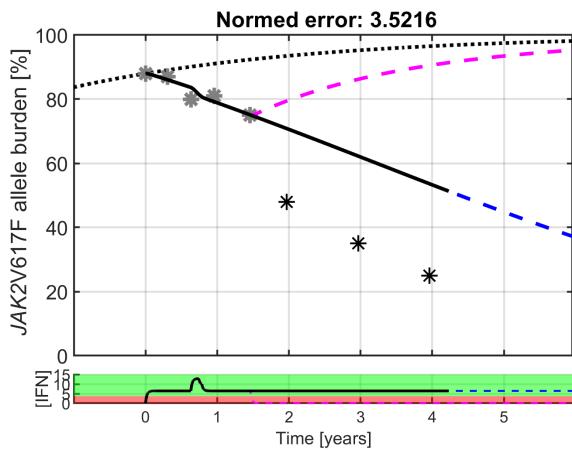


Patient P125

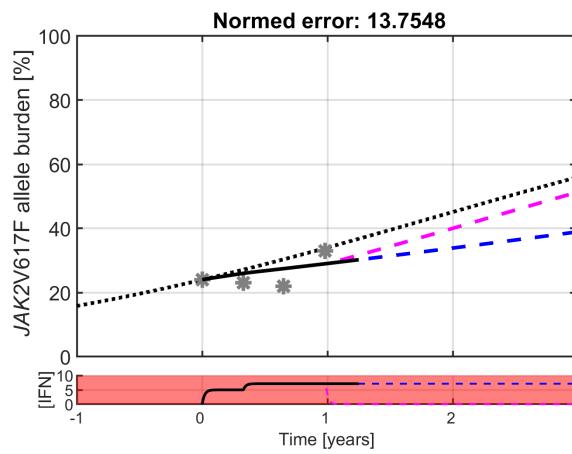
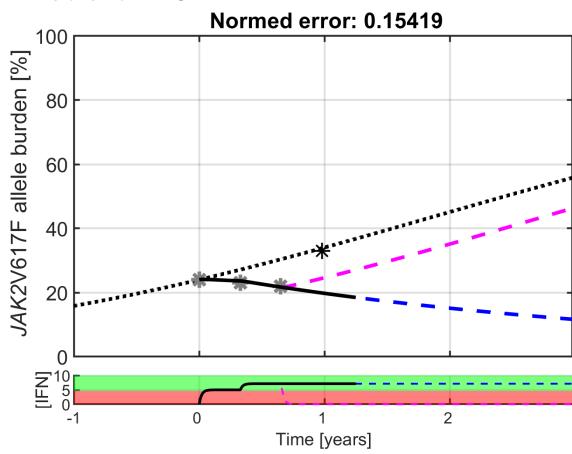


Patient P129

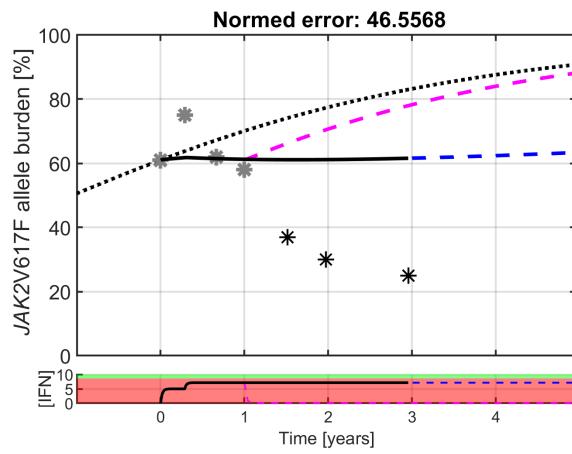
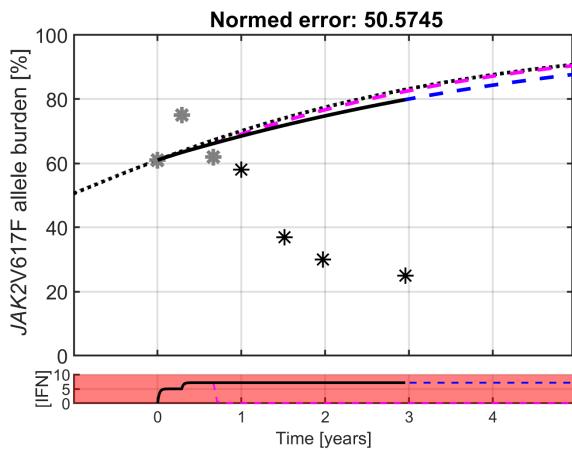


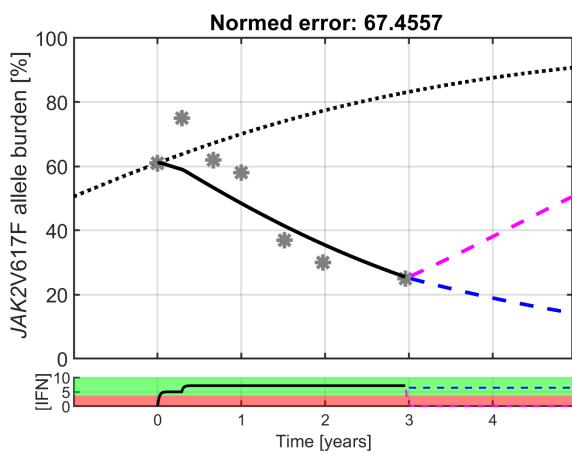
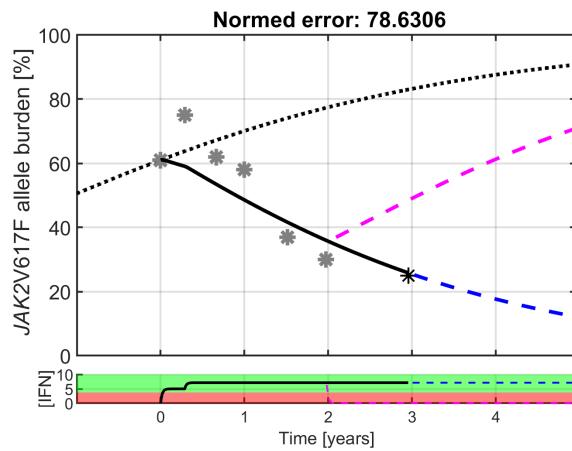
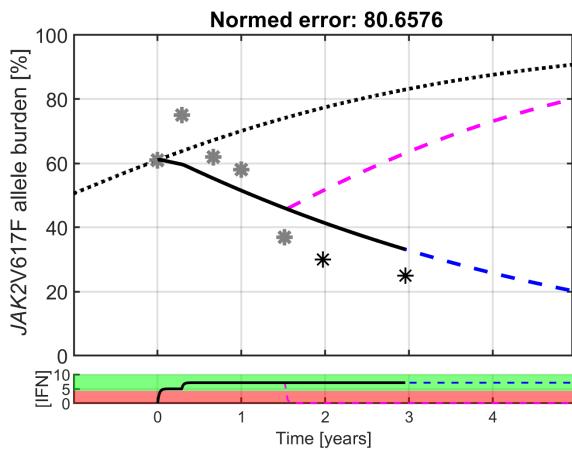


Patient P131

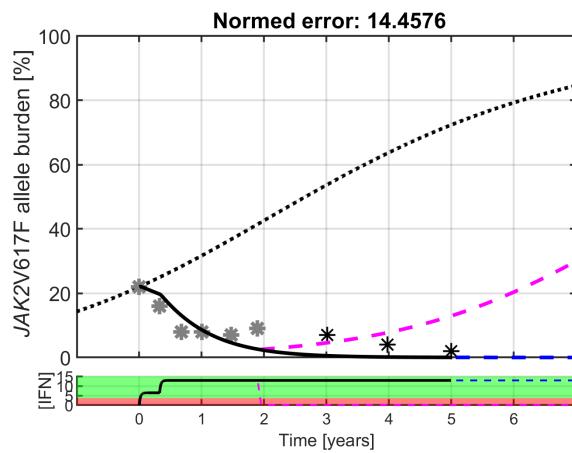
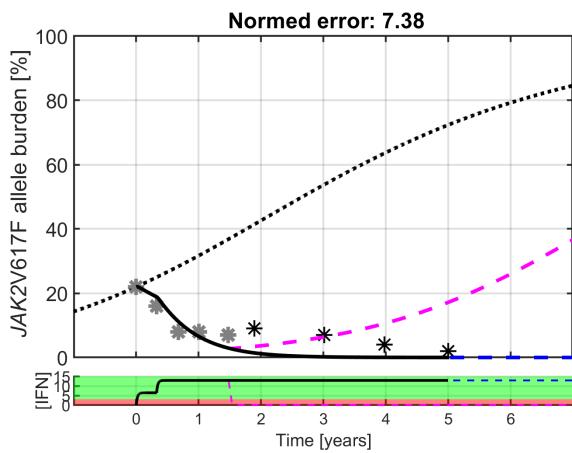
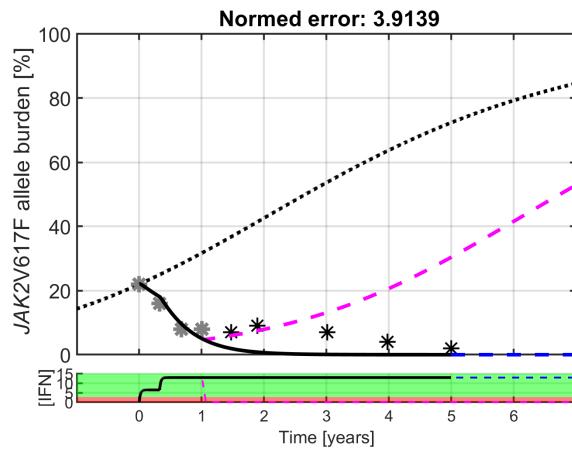
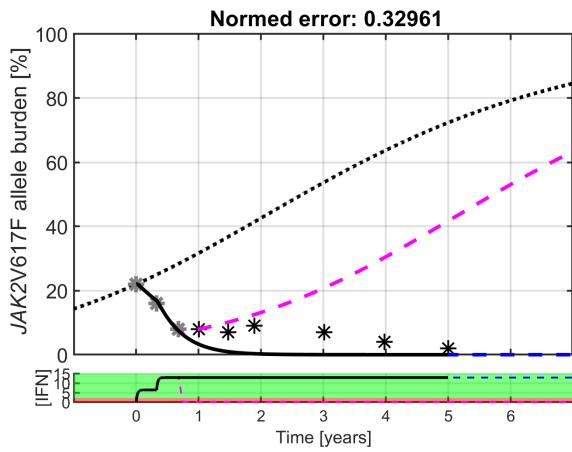


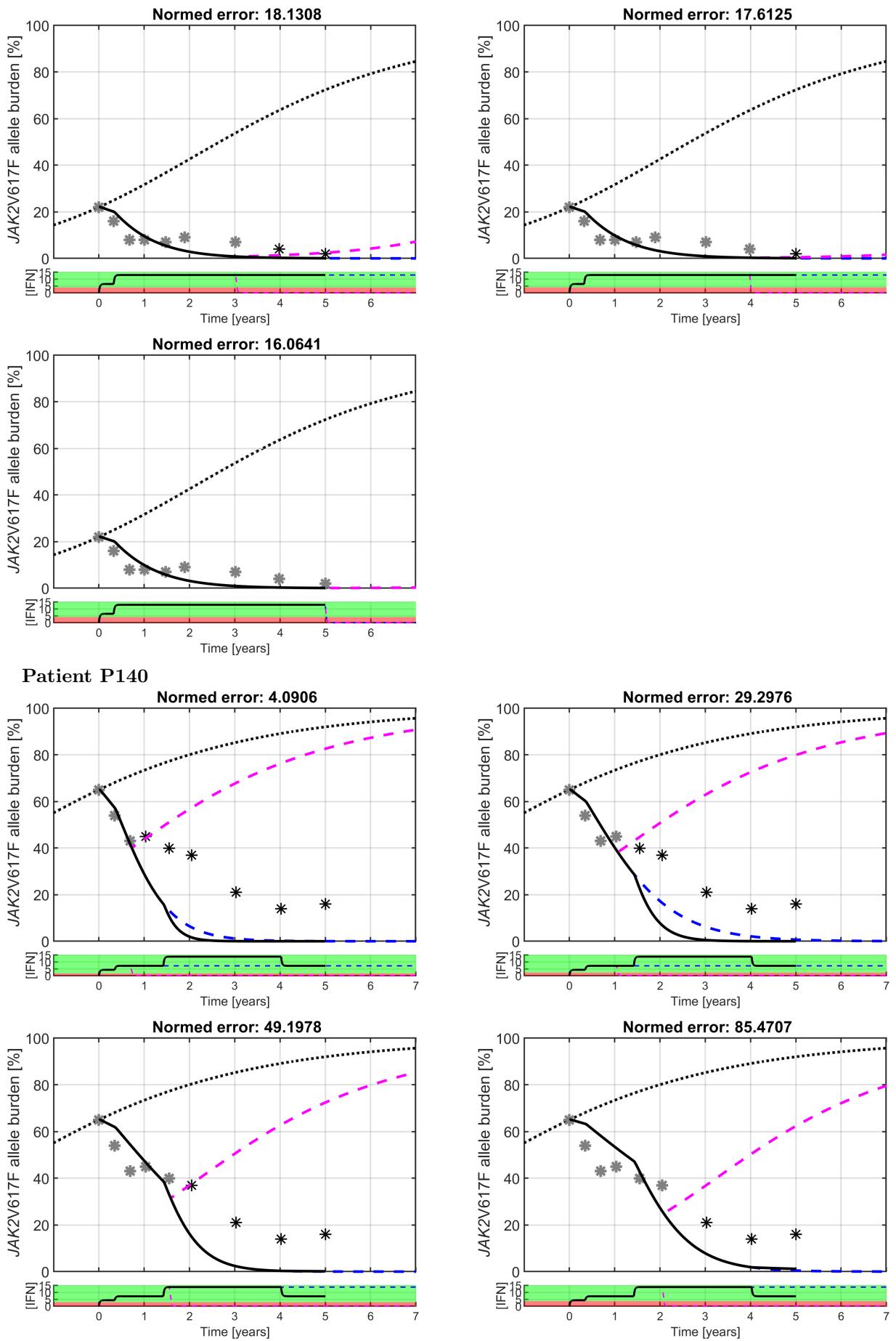
Patient P135

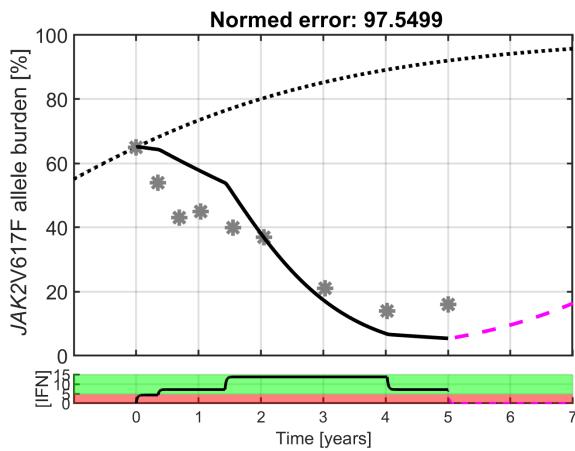
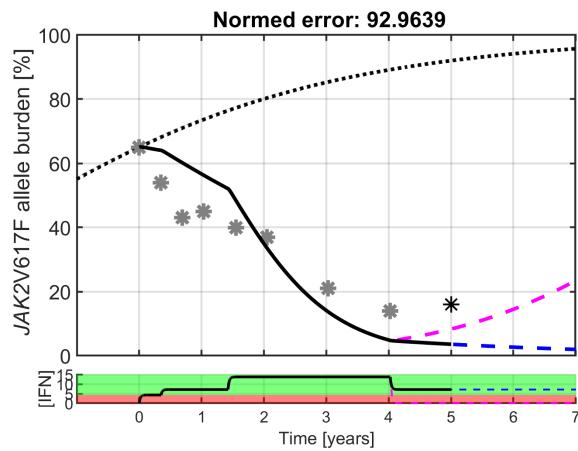
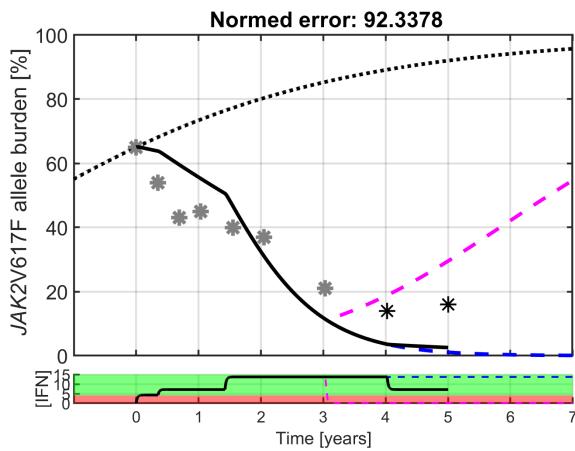




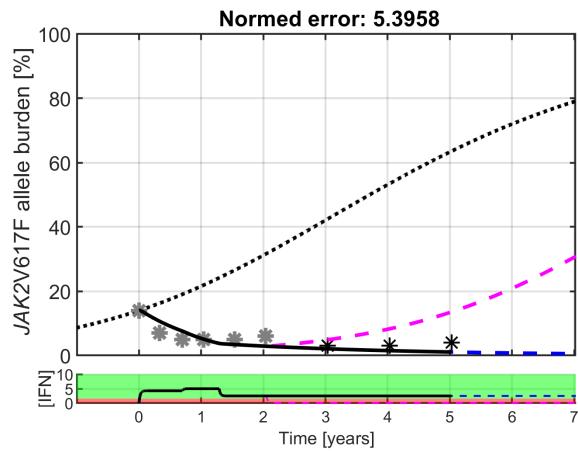
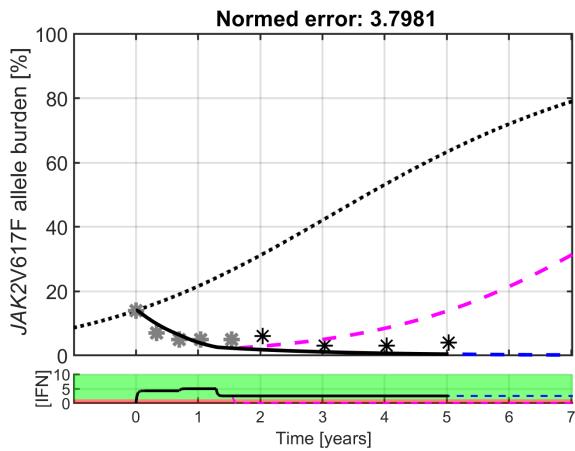
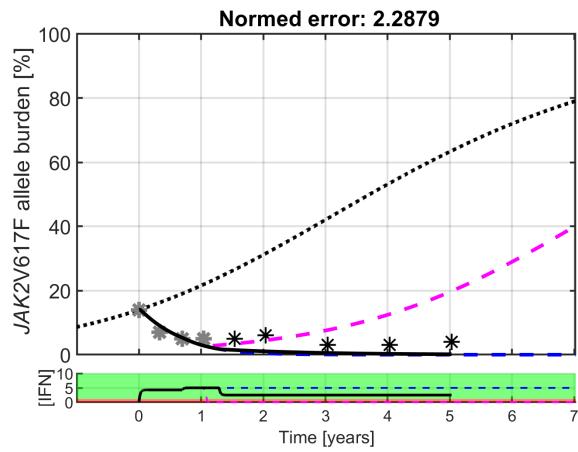
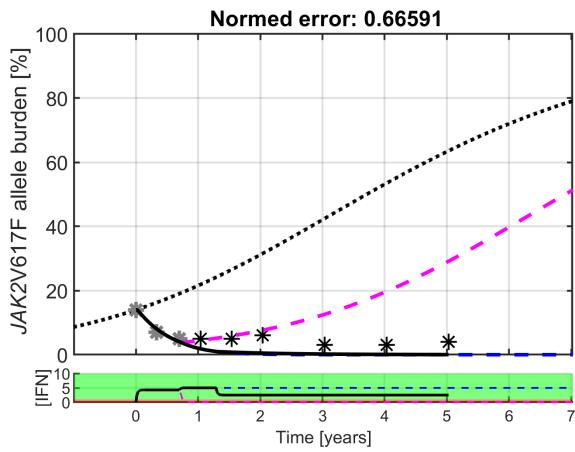
### Patient P139

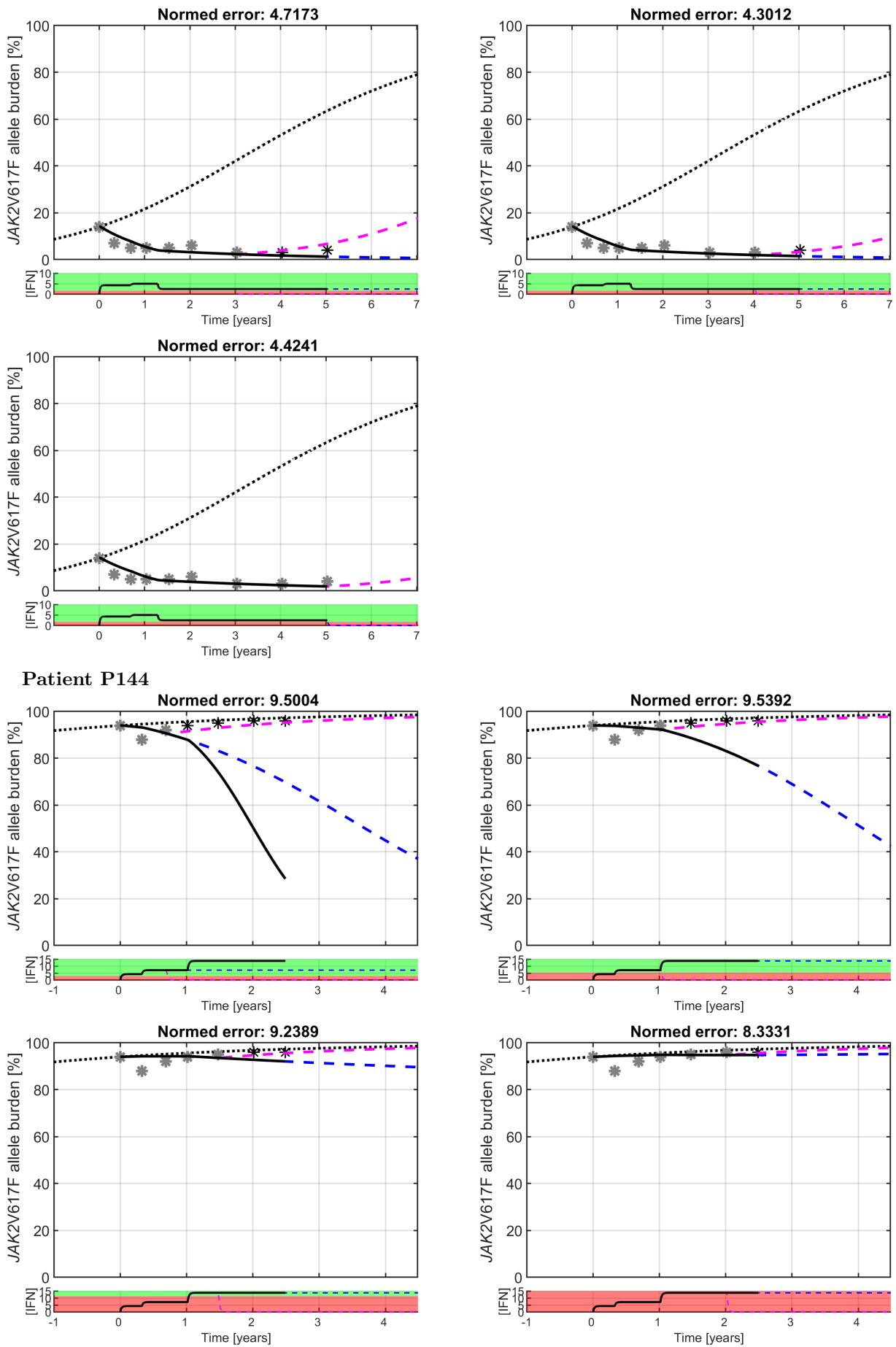


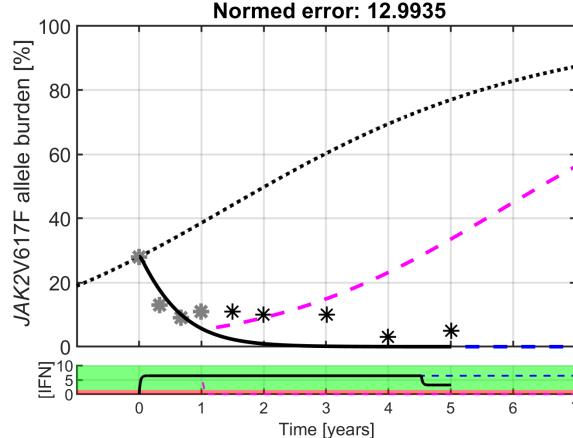
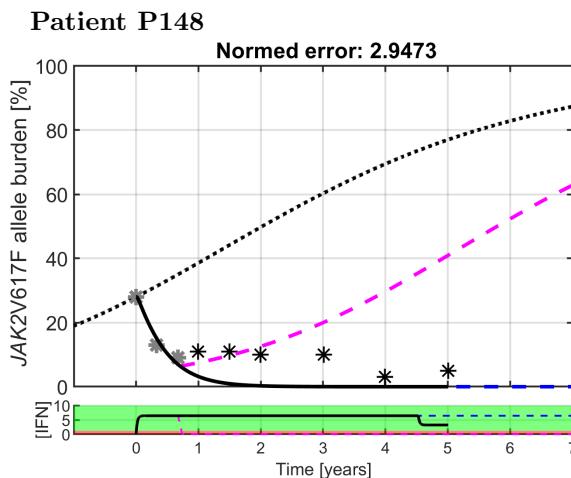
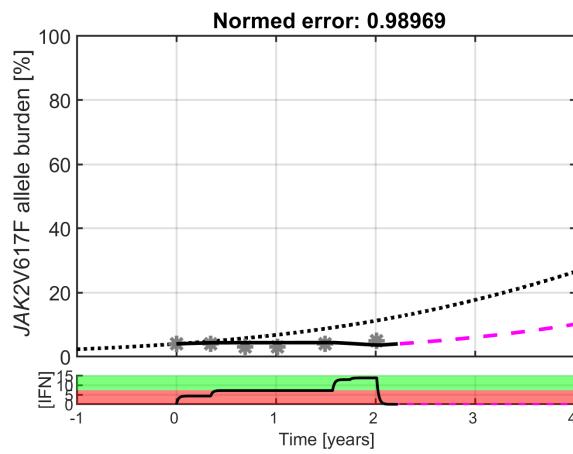
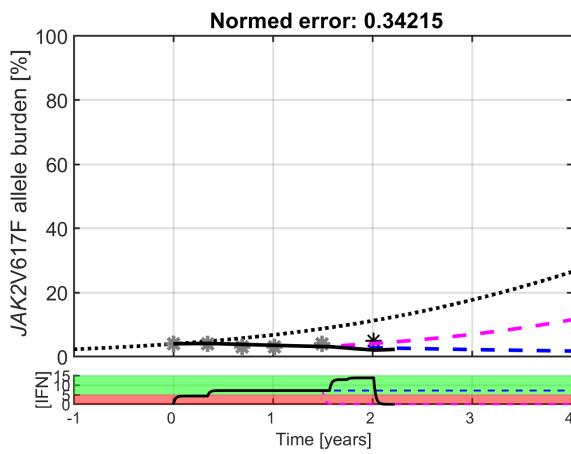
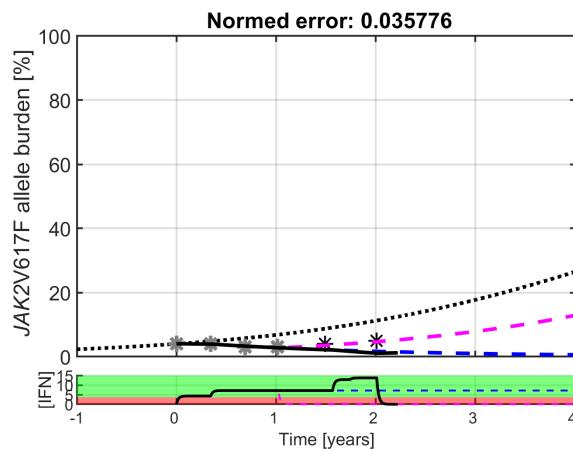
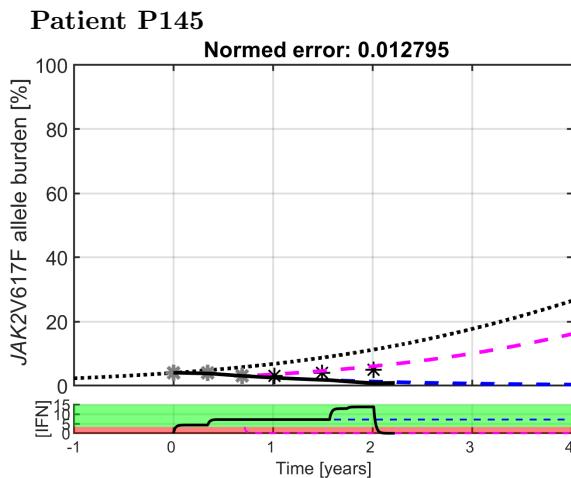
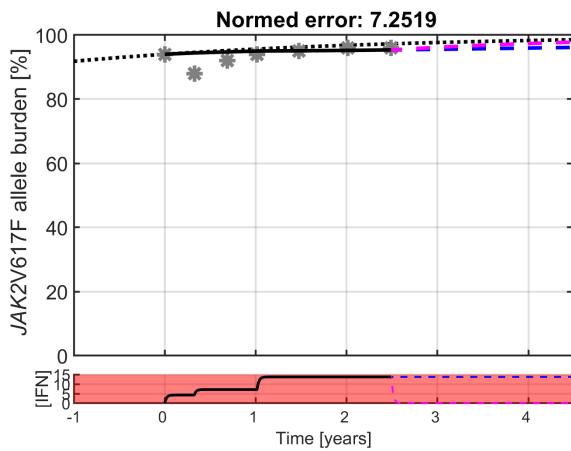


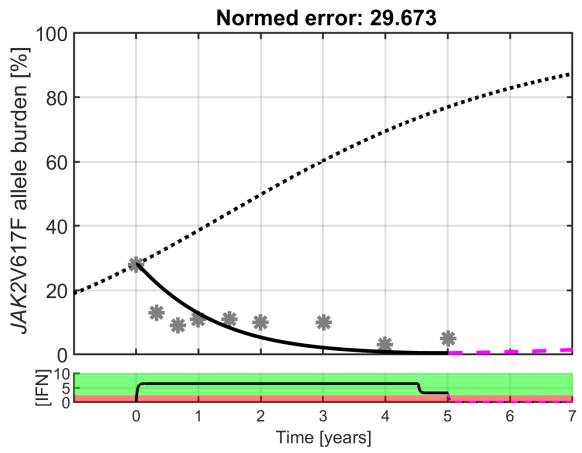
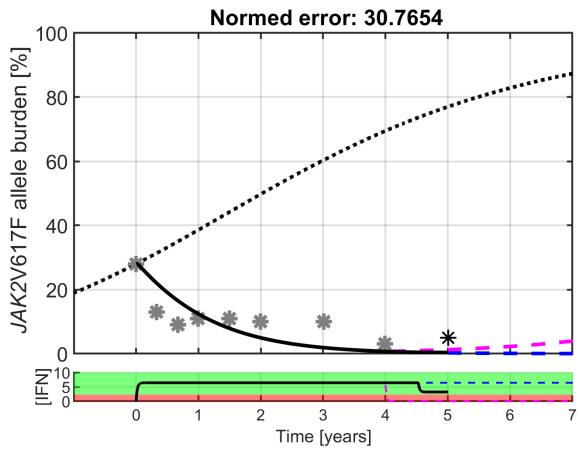
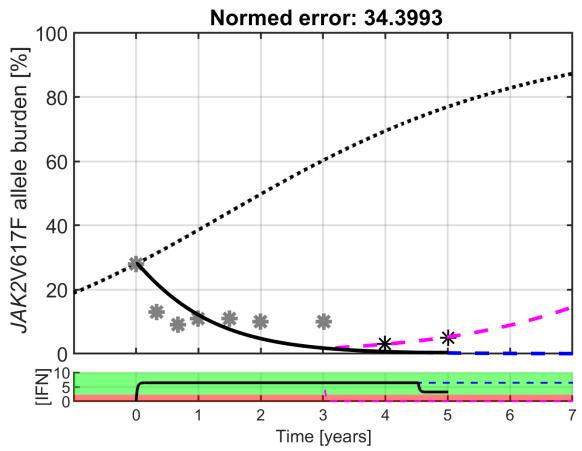
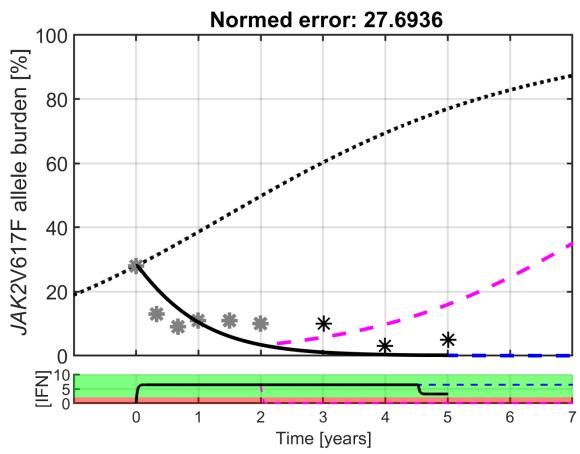
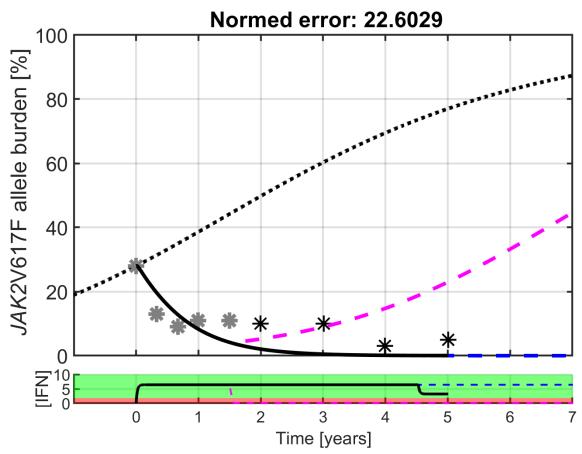


#### Patient P142

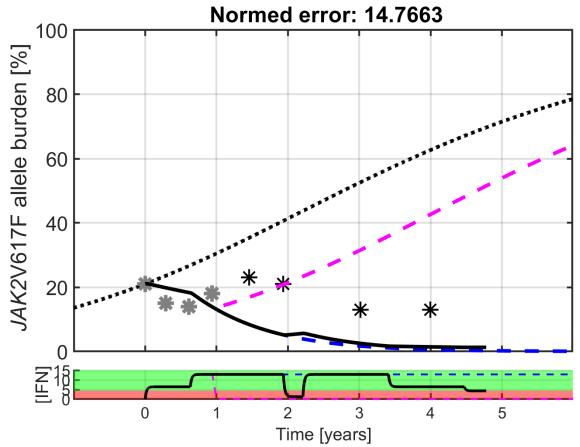
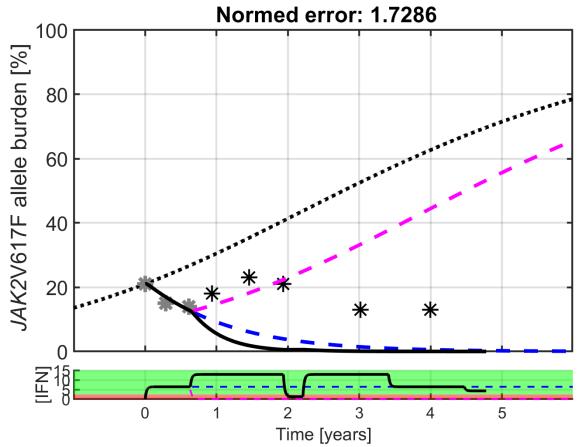


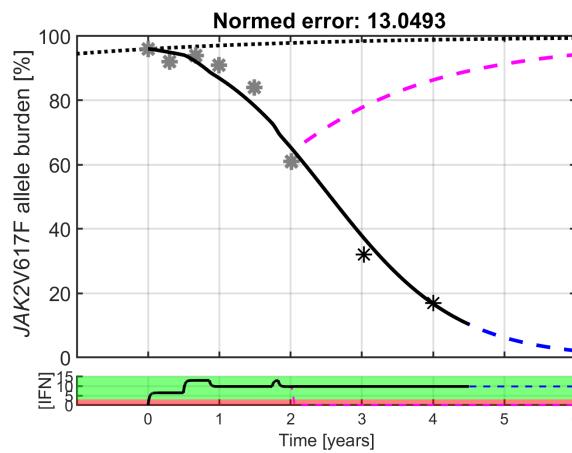
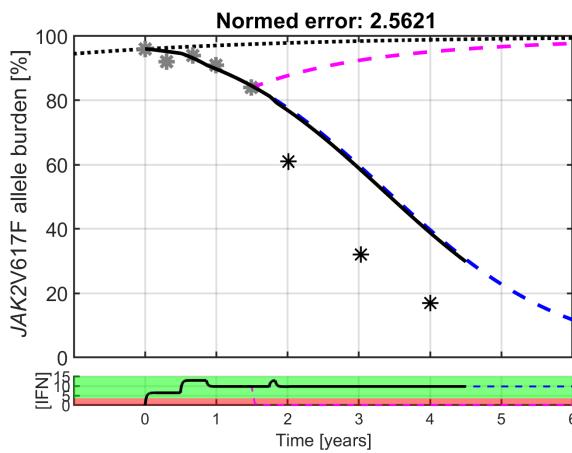
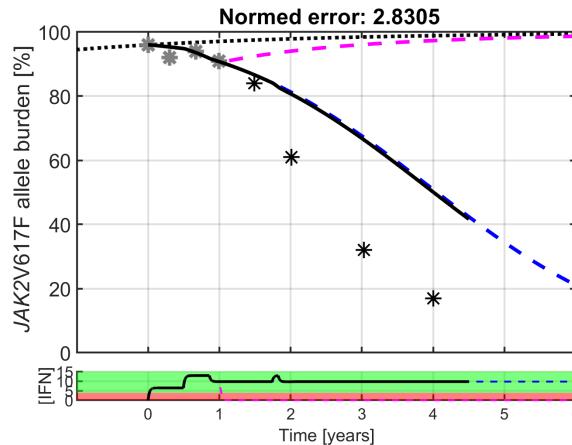
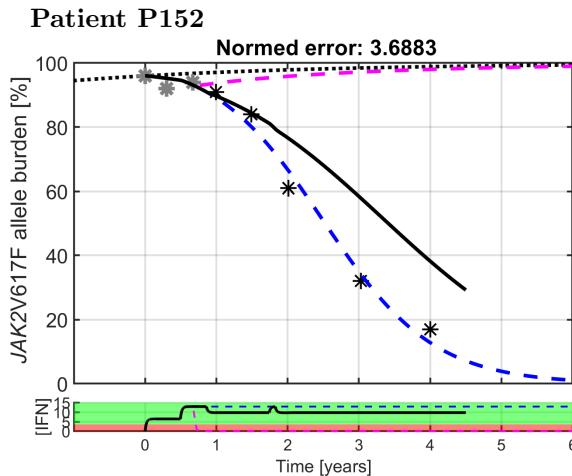
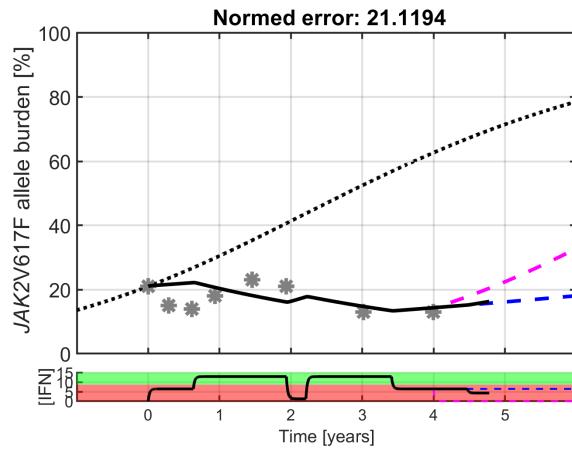
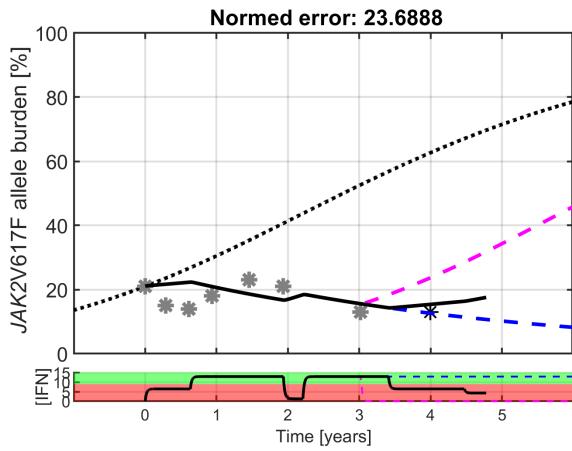
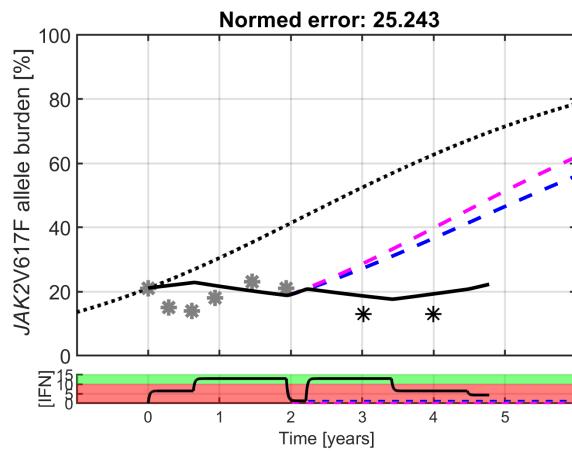
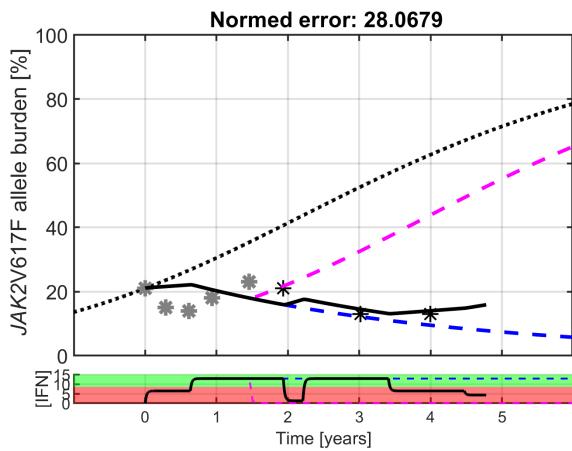


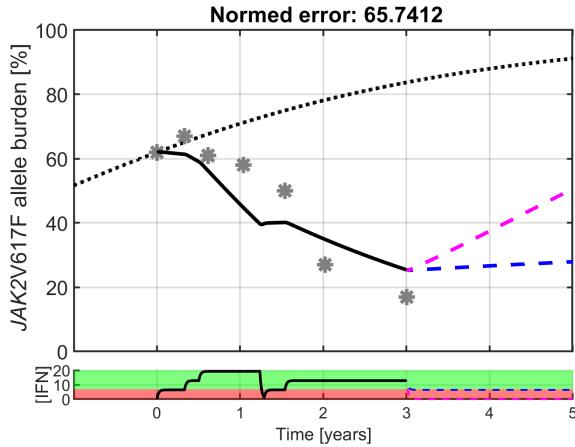
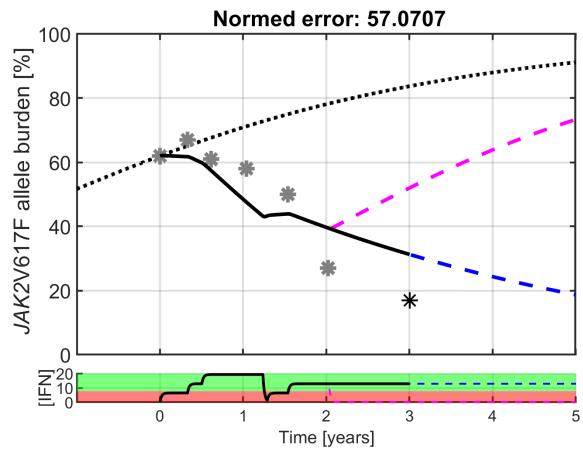
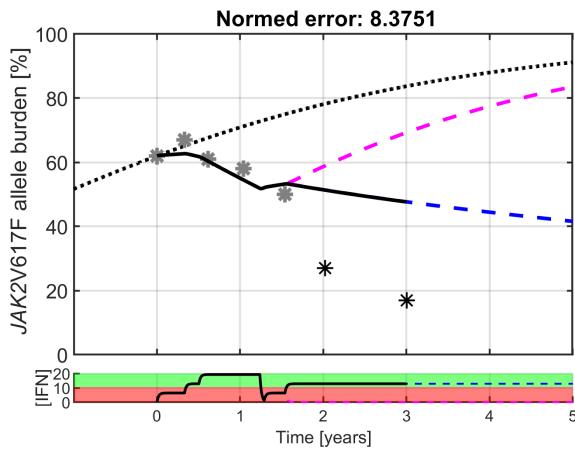
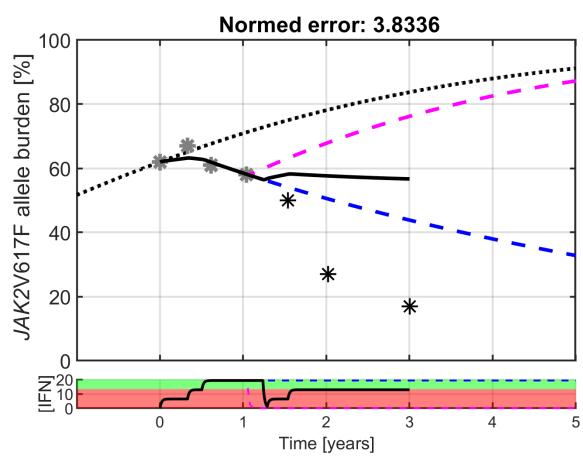
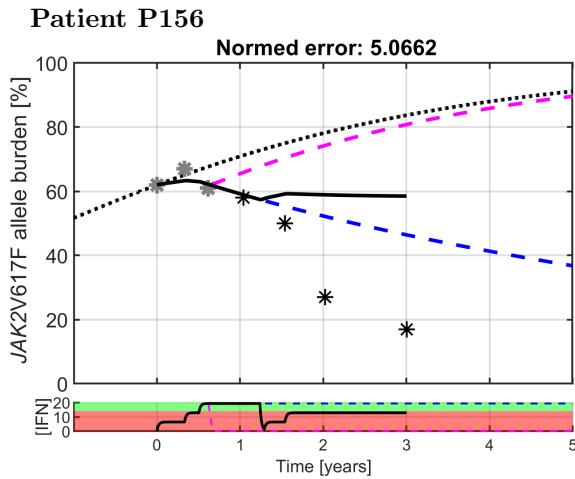
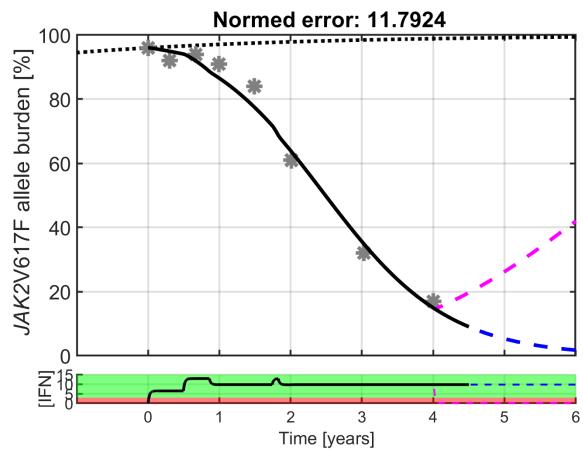
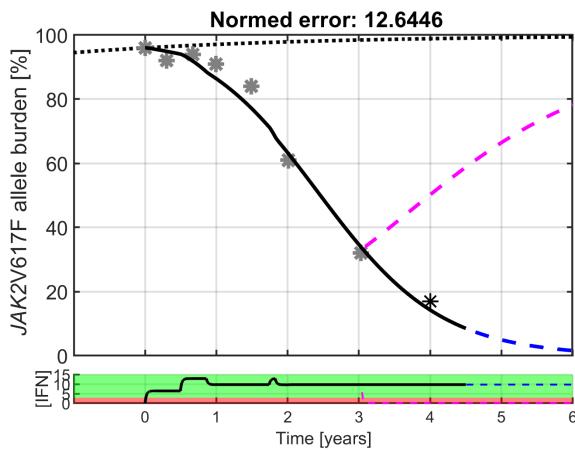




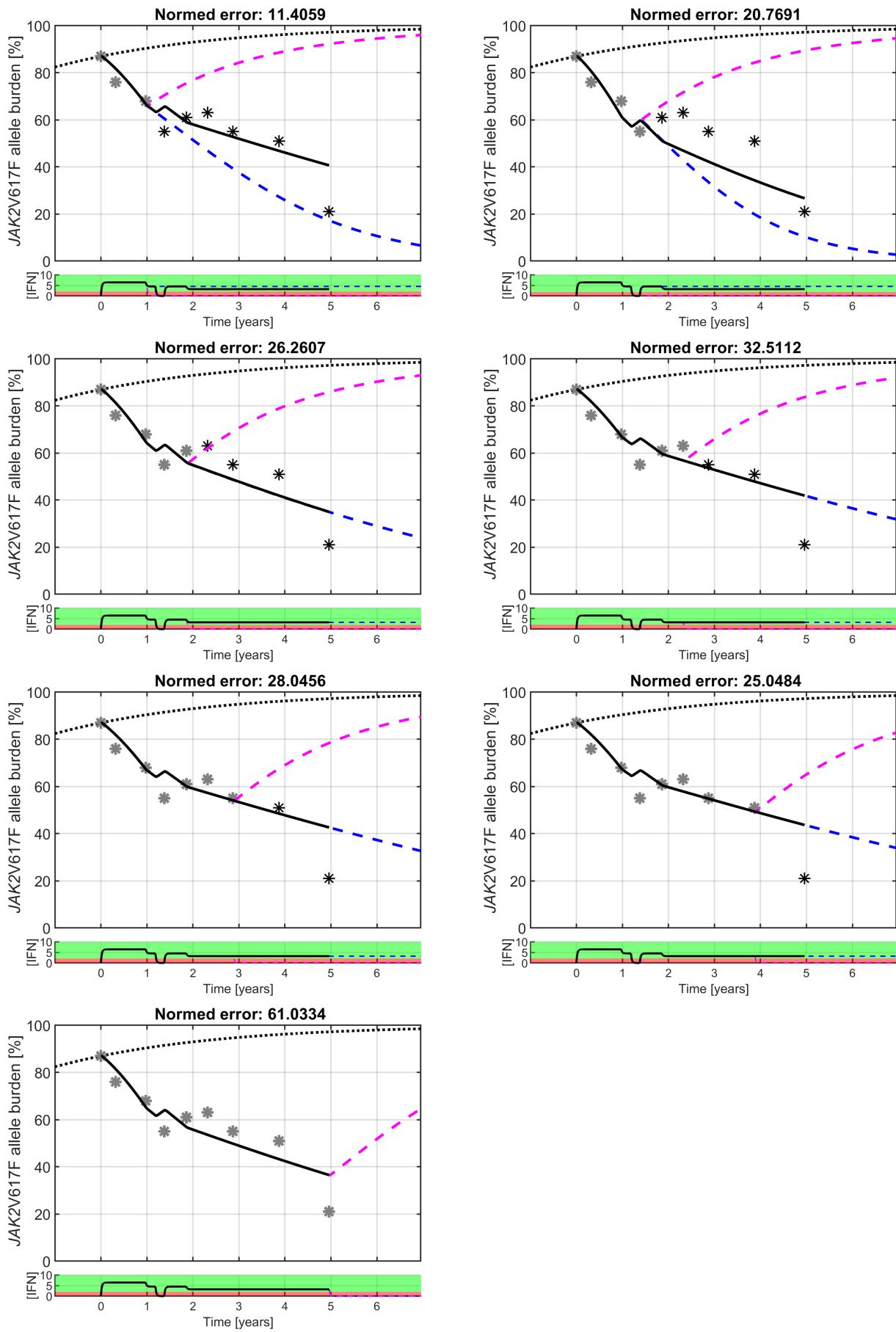
### Patient P150

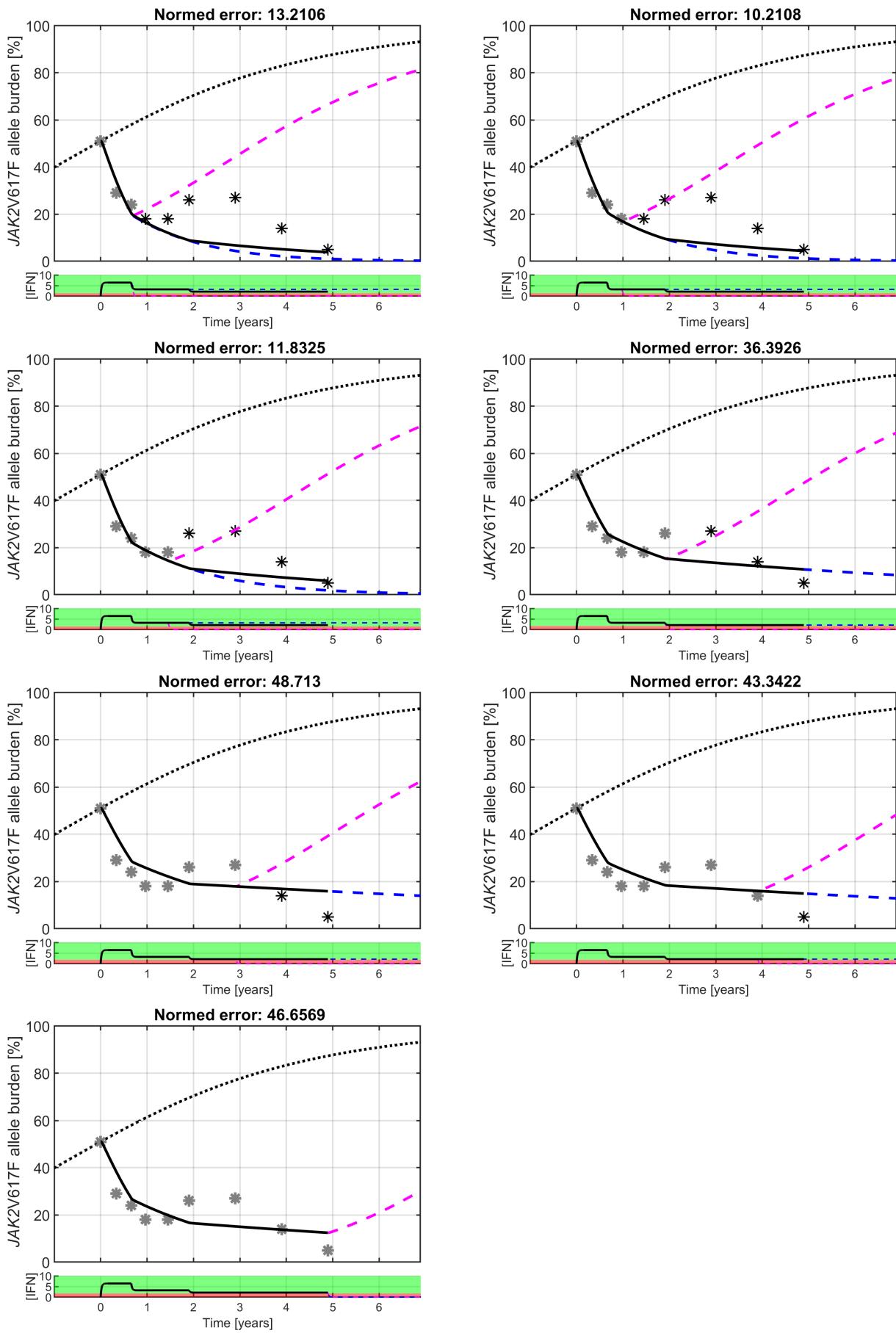


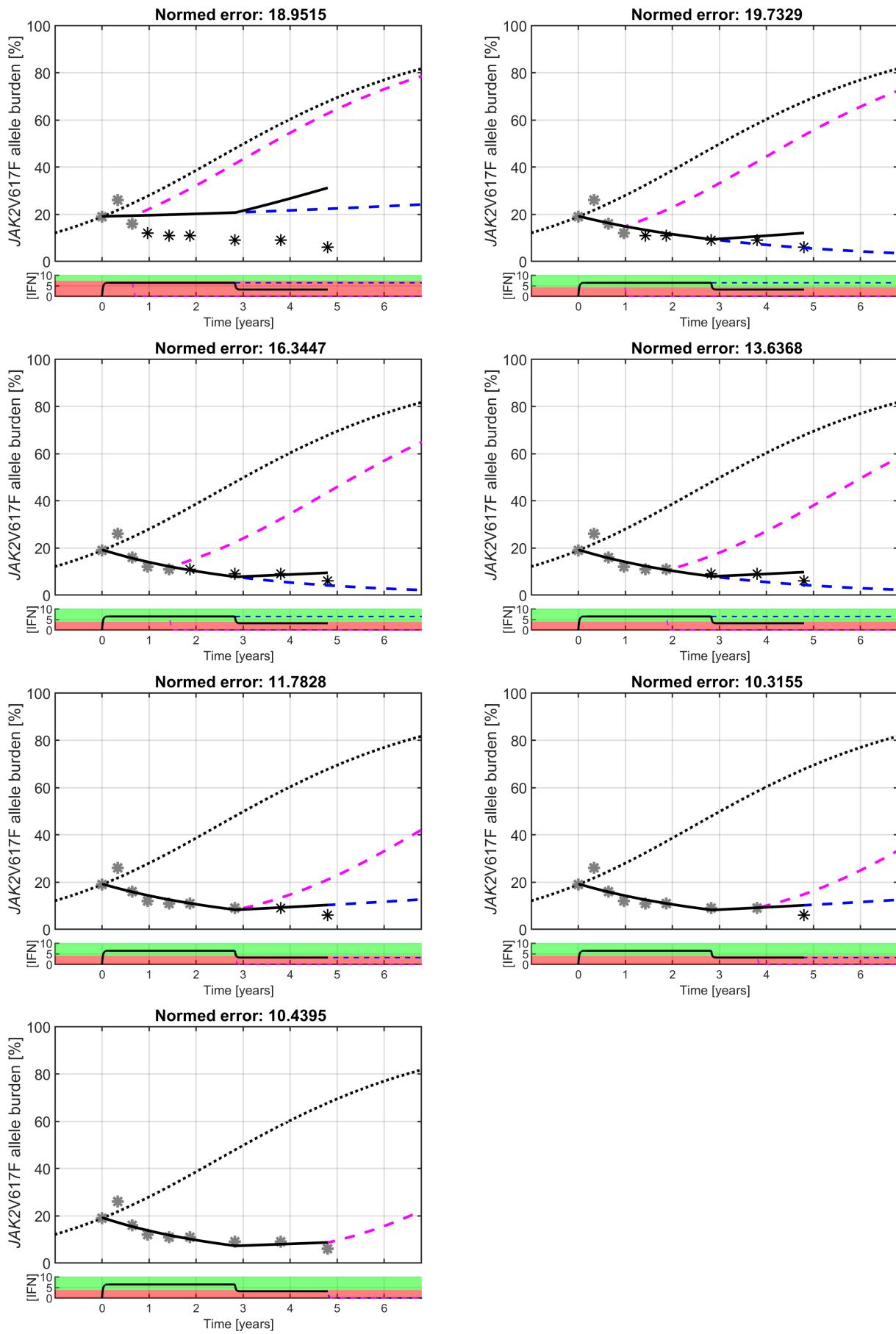




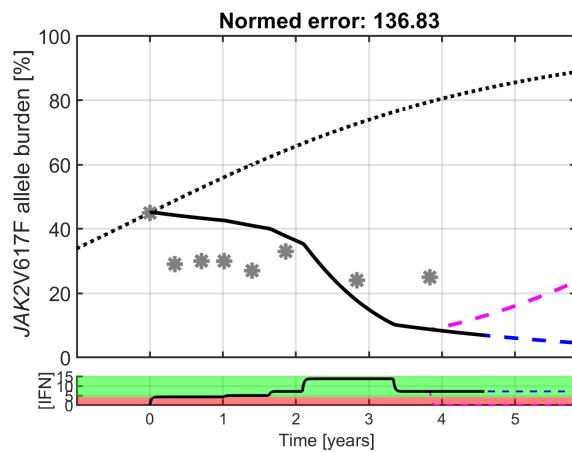
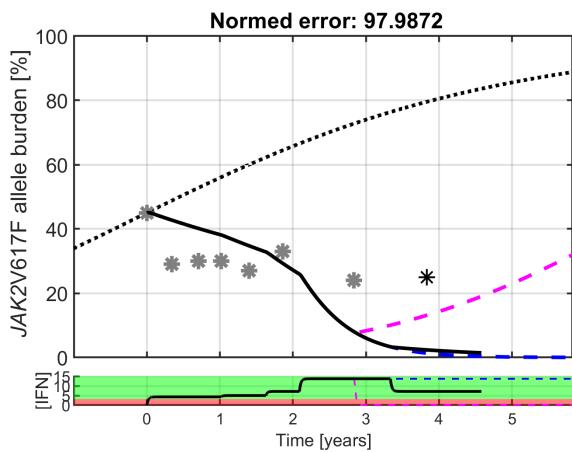
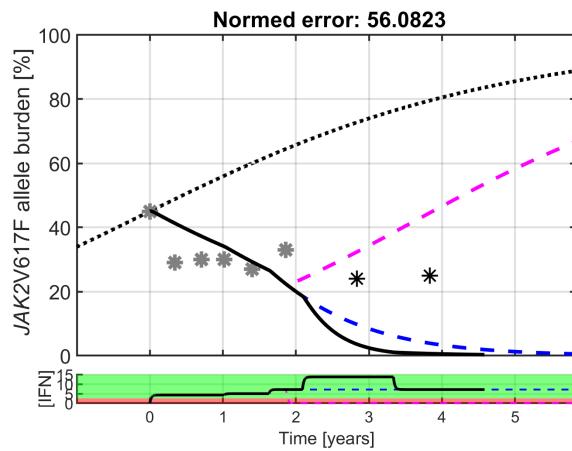
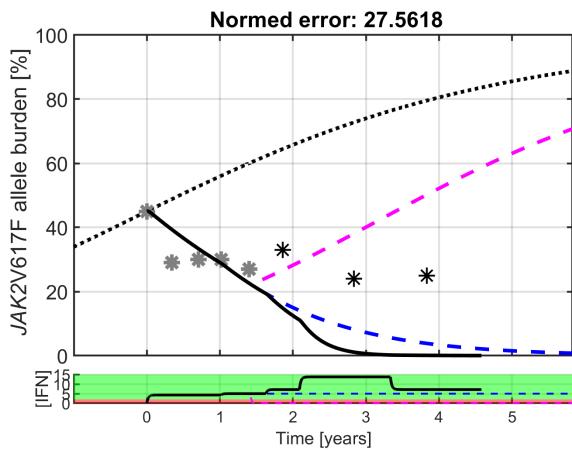
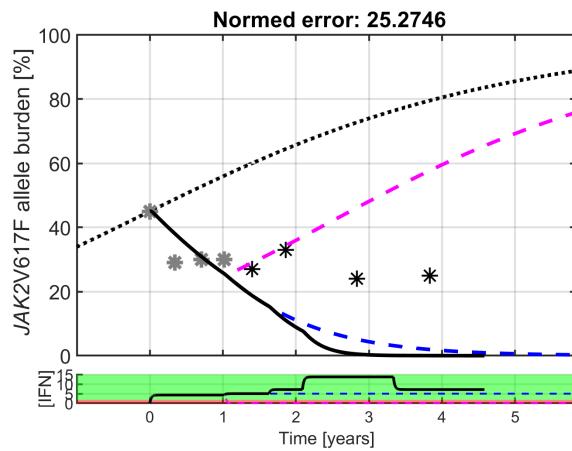
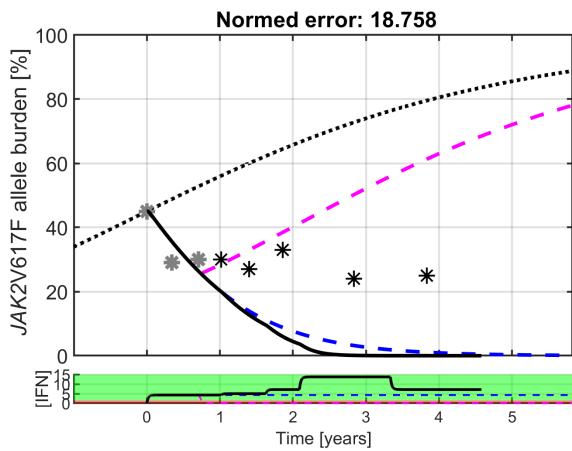
**Patient P158**



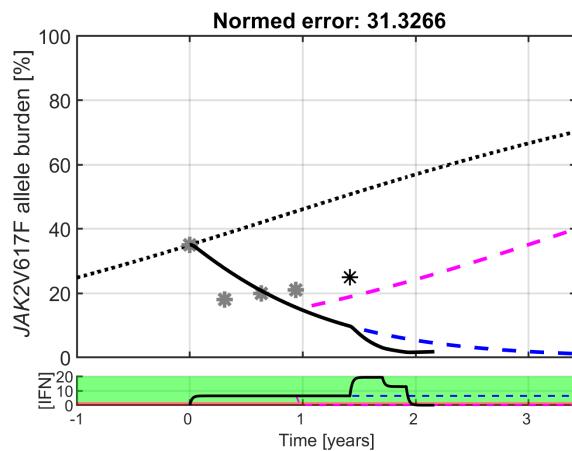
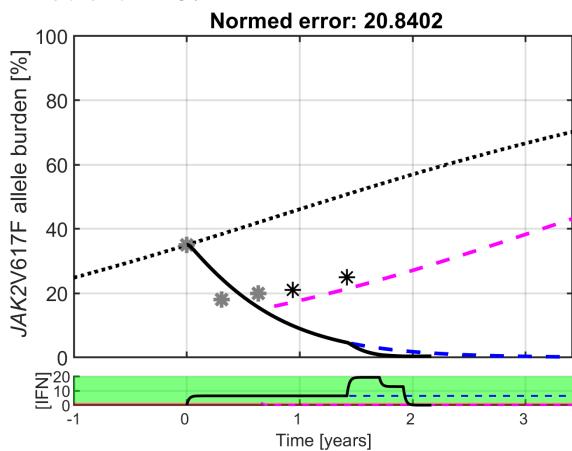


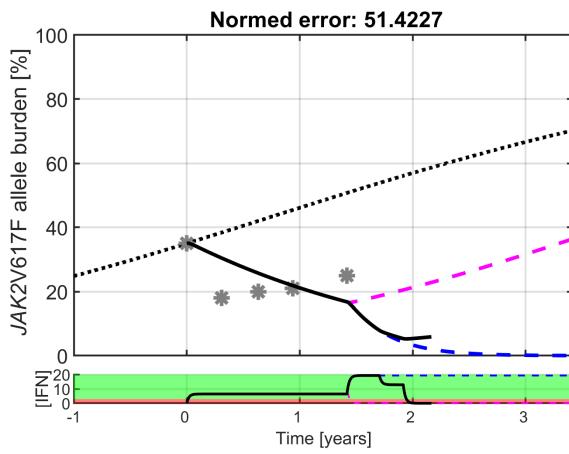


Patient P164

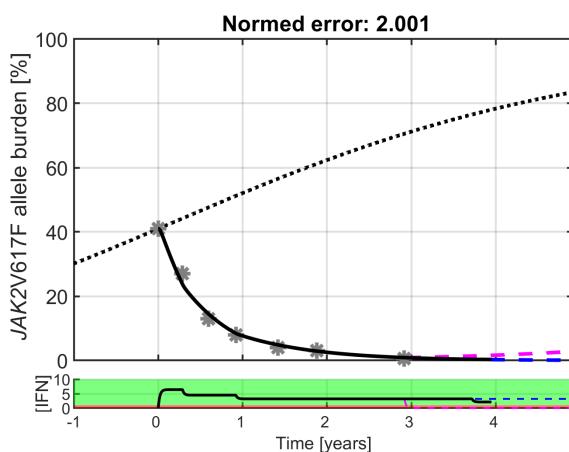
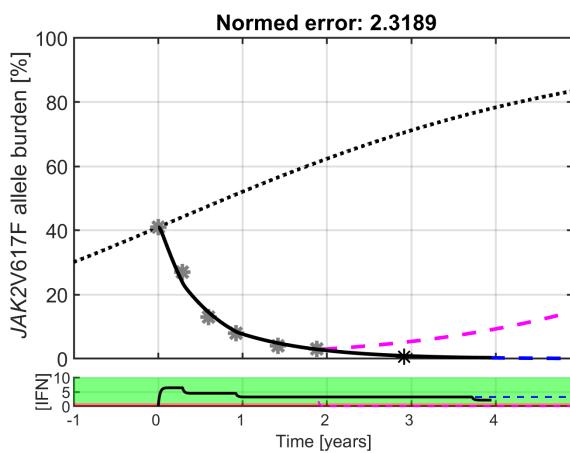
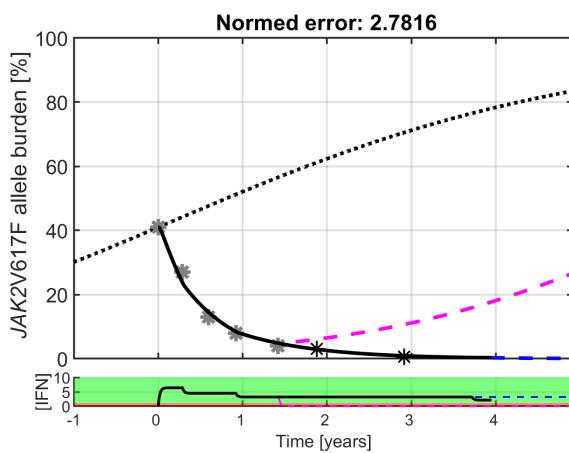
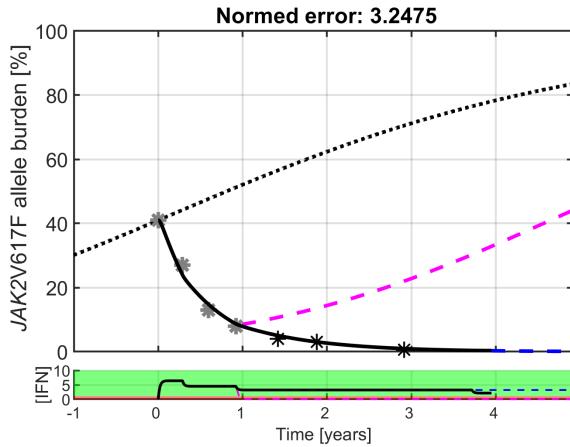
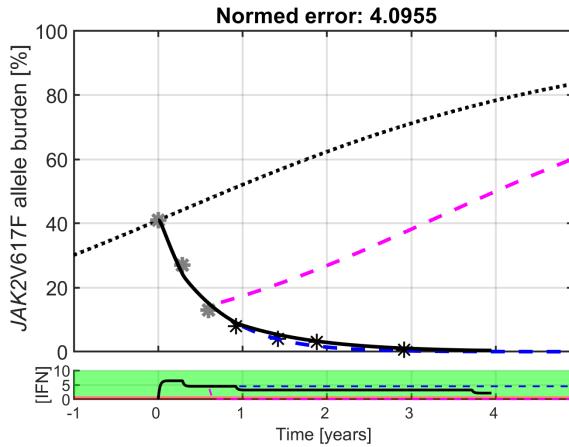


### Patient P167

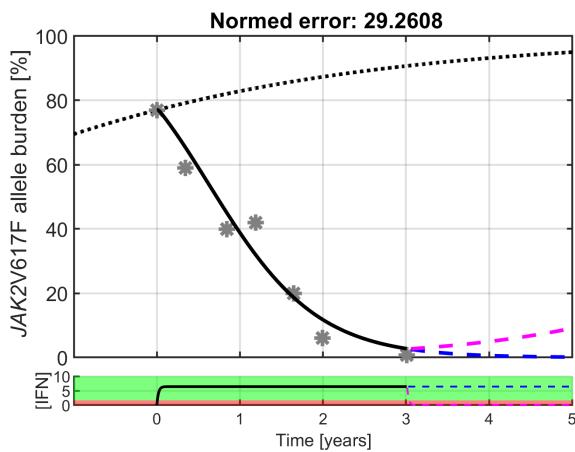
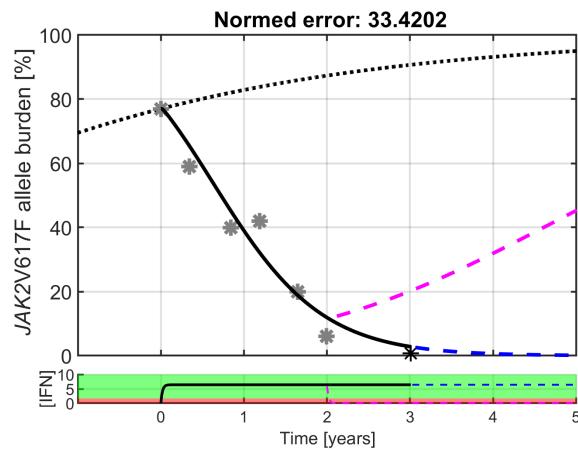
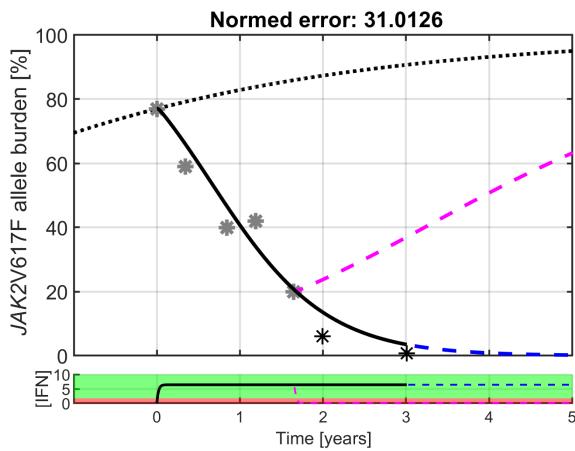
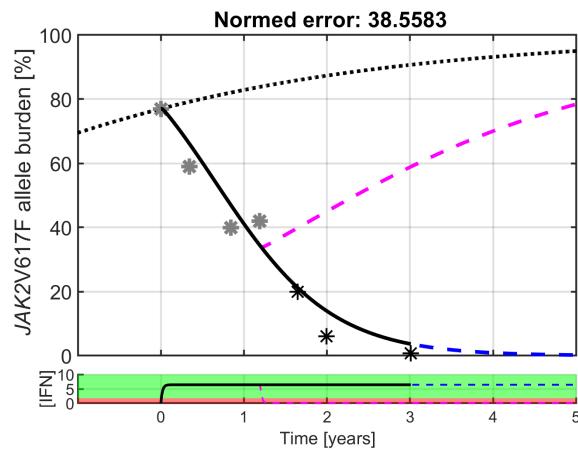
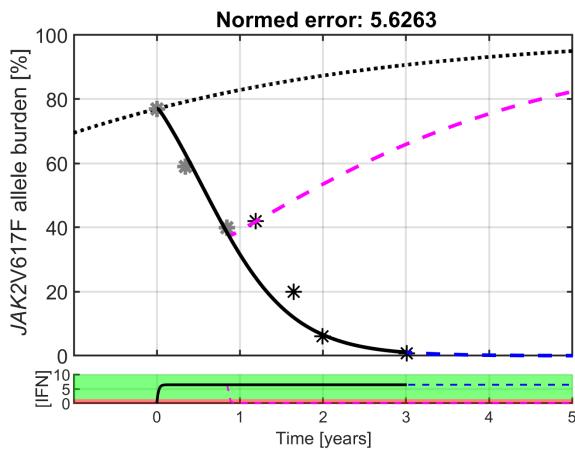




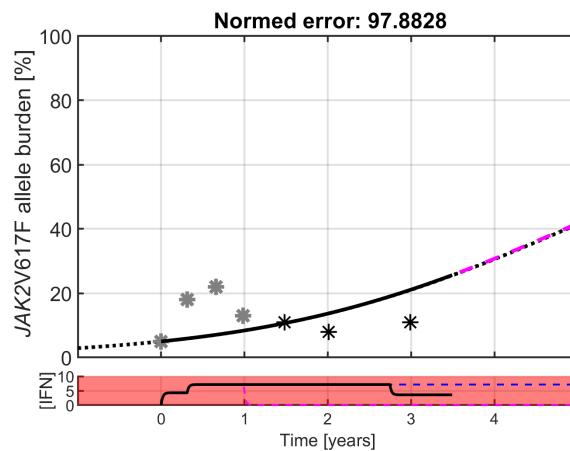
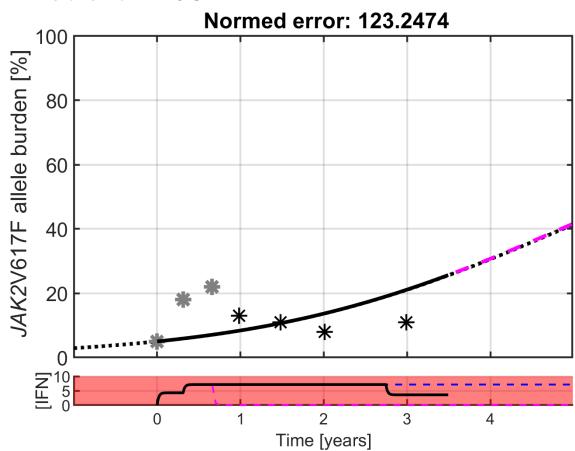
Patient P184

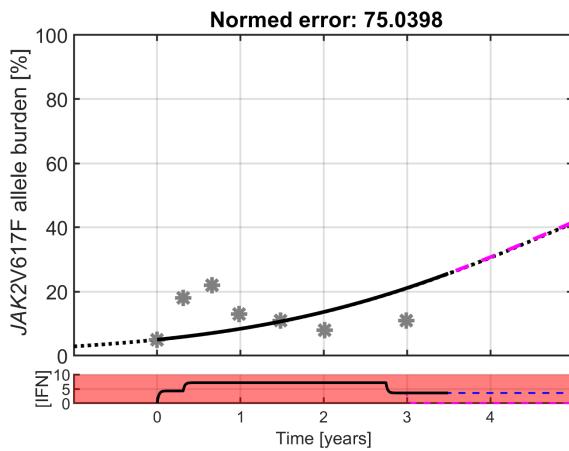
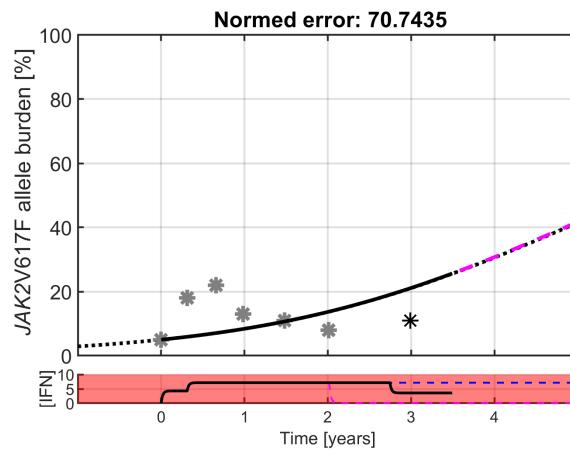
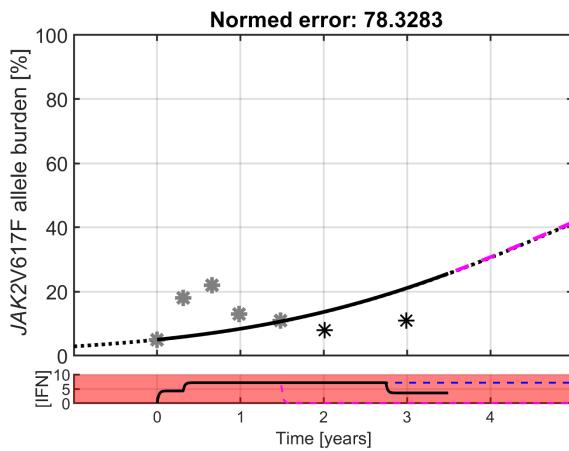


Patient P187

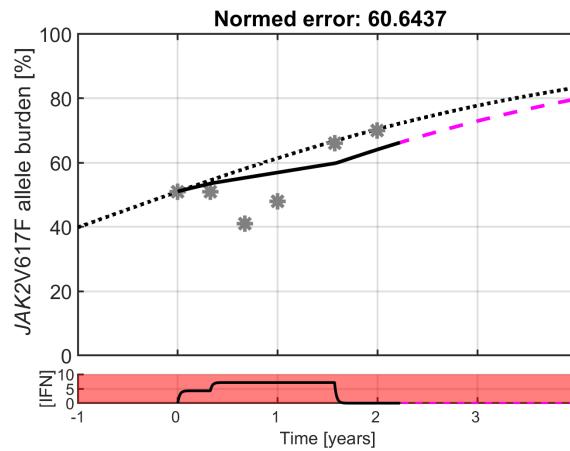
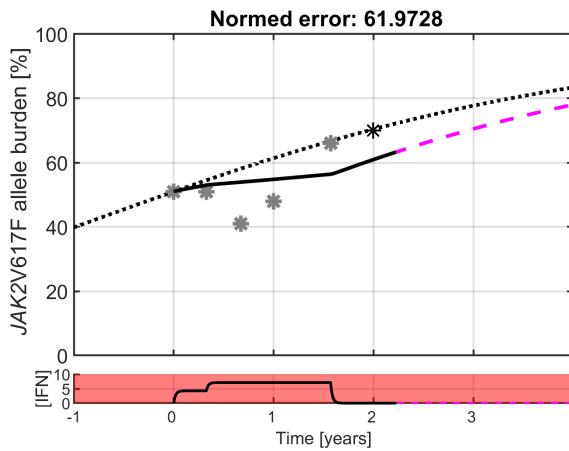
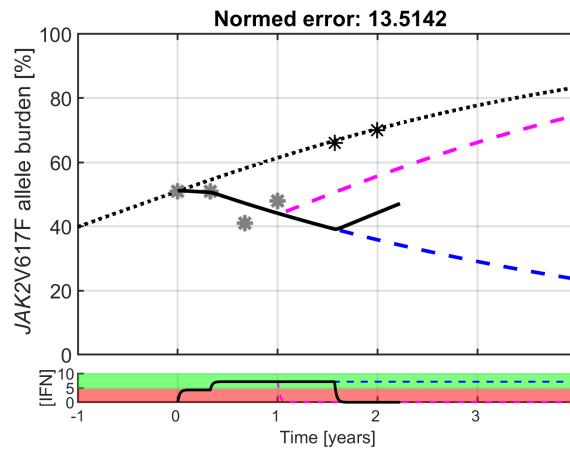
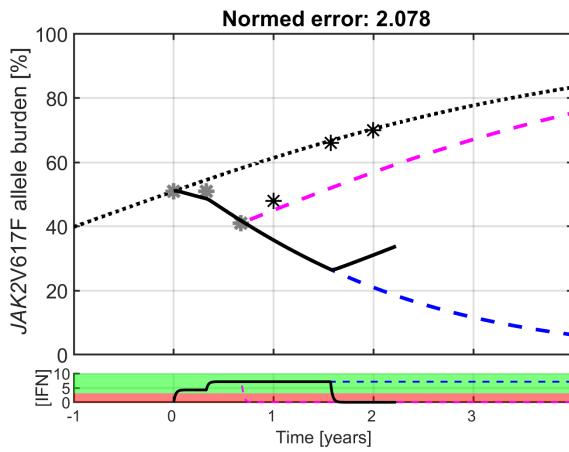


### Patient P190

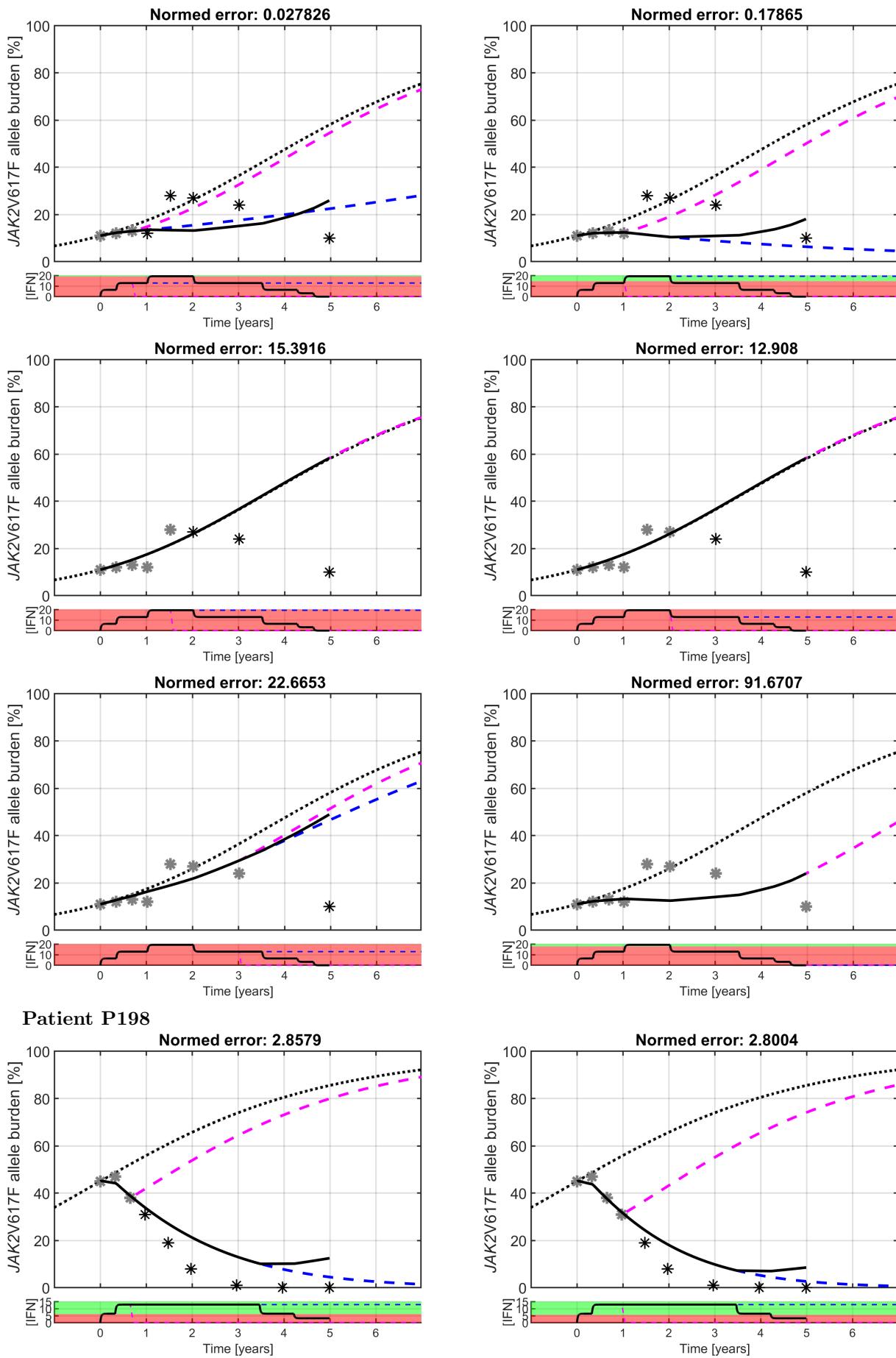


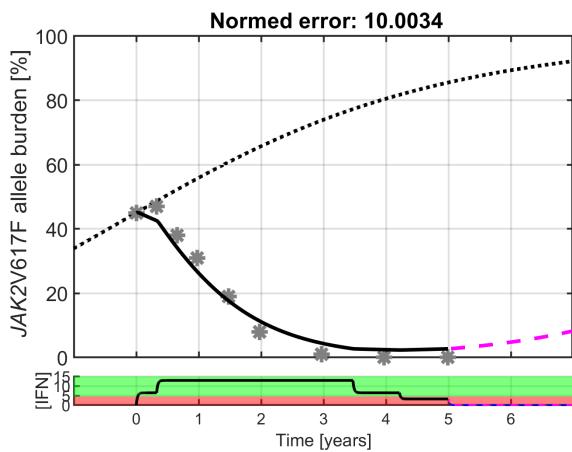
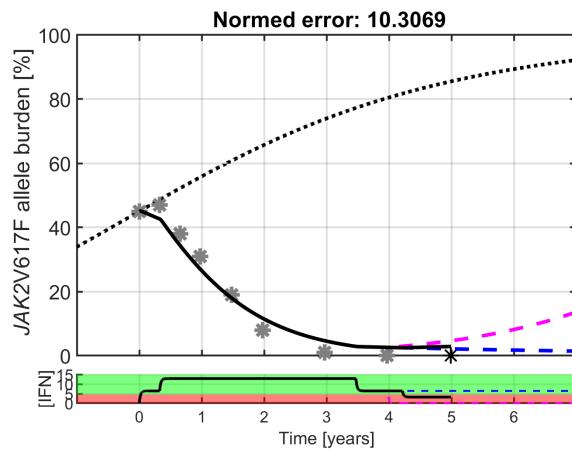
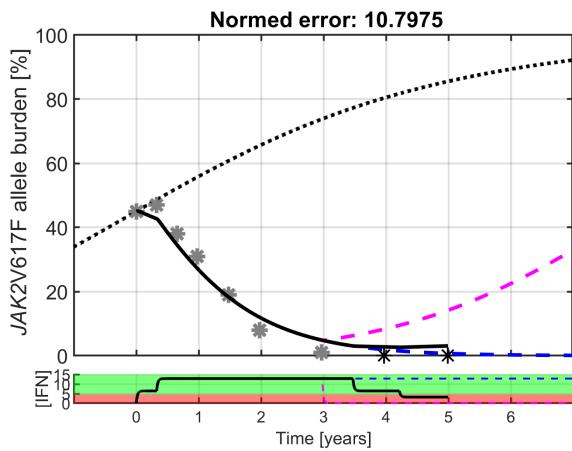
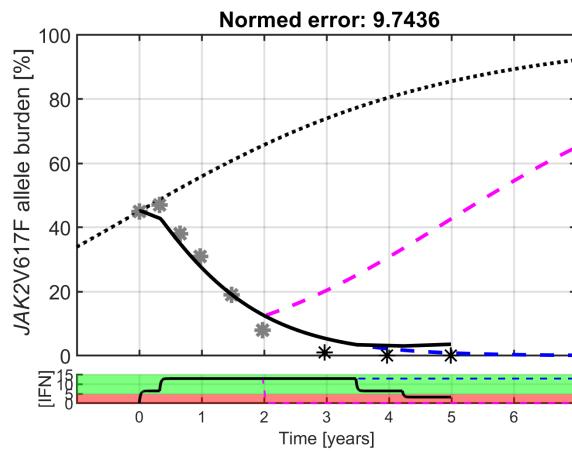
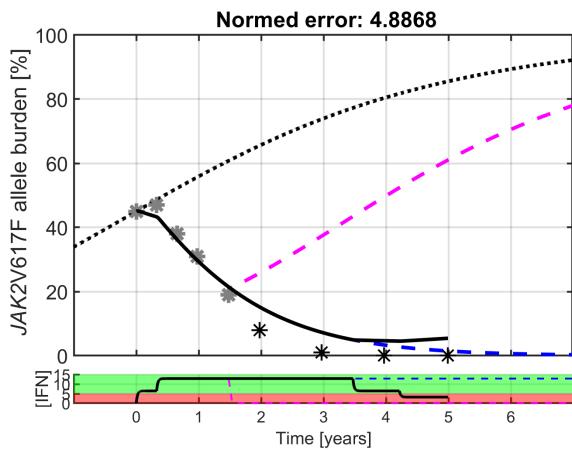


Patient P196

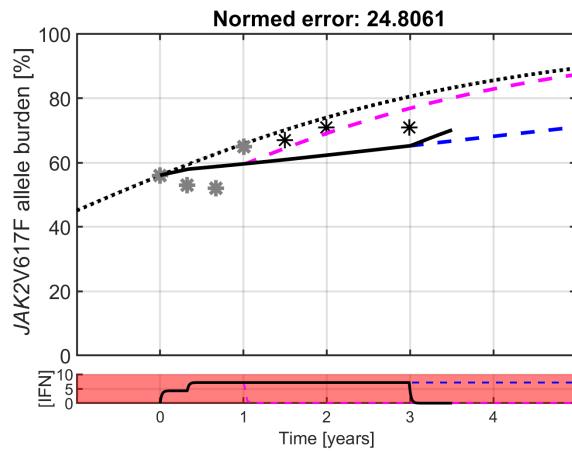
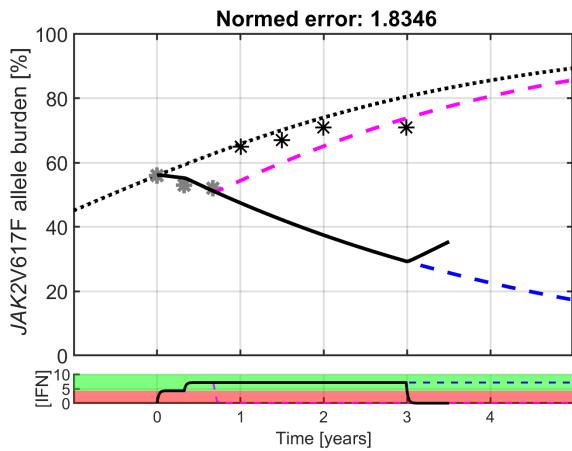


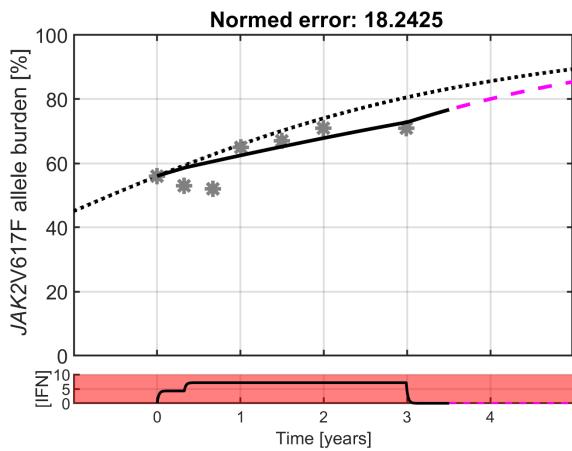
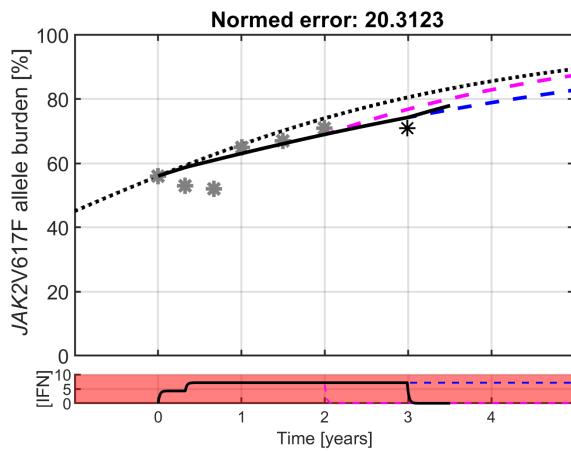
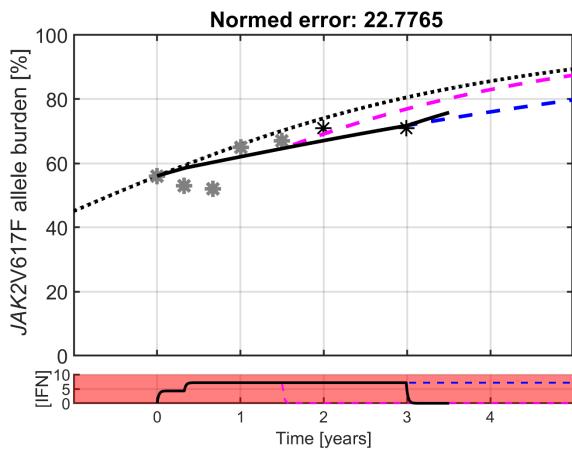
Patient P197



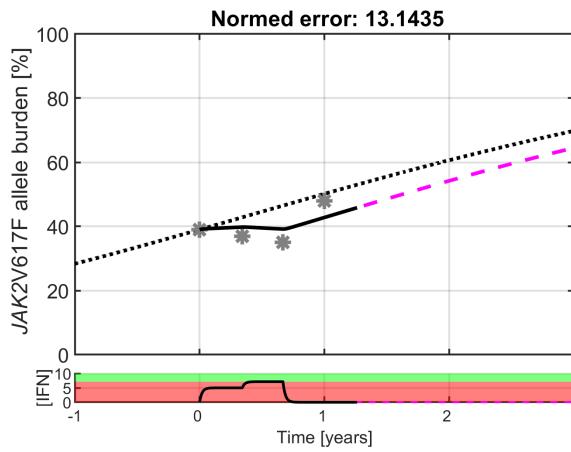
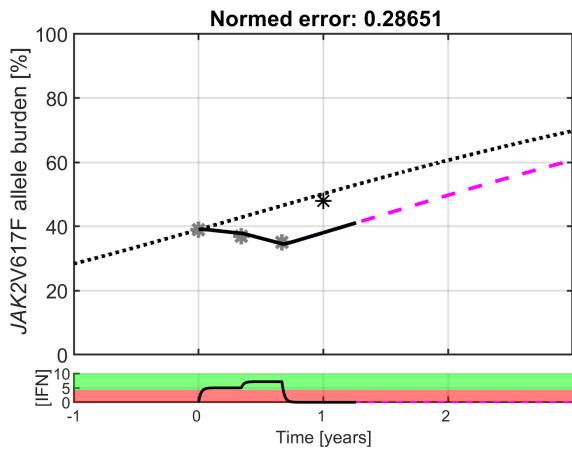


Patient P199

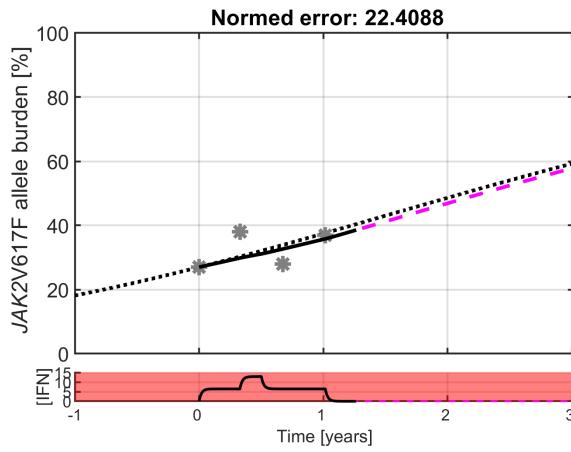
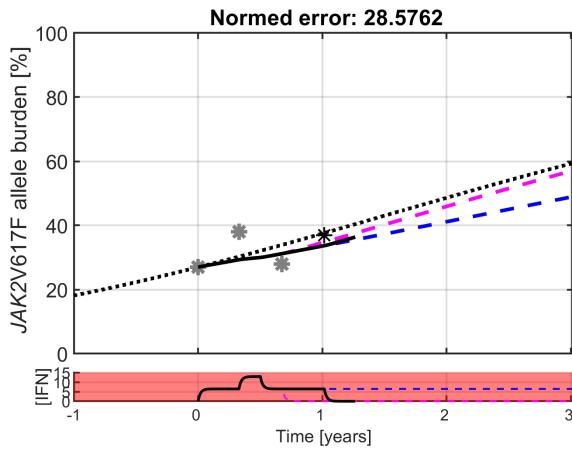




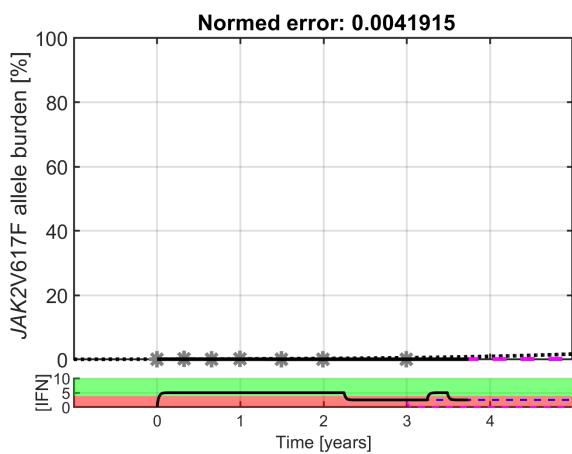
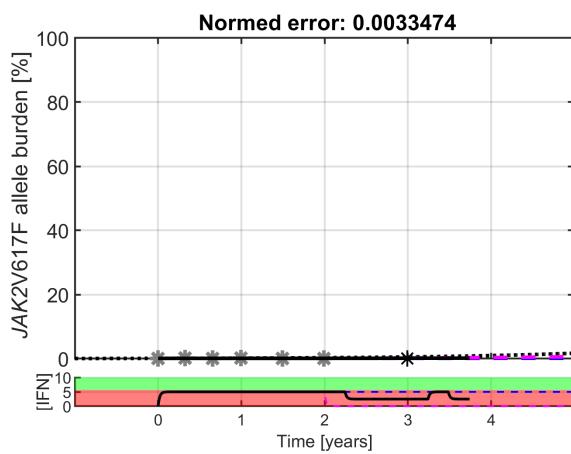
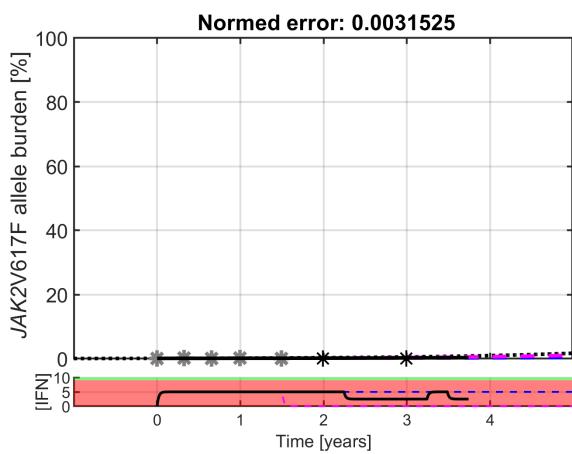
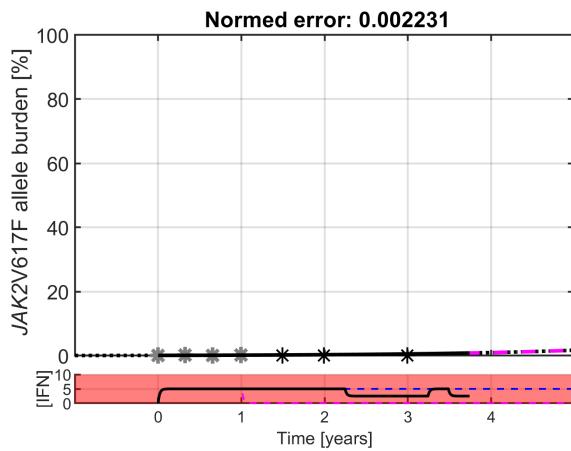
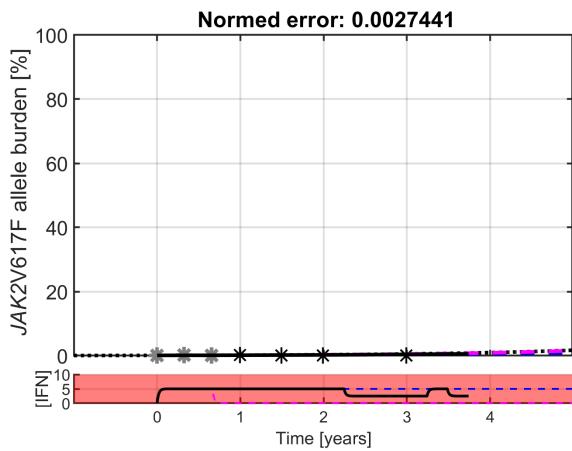
**Patient P201**



**Patient P202**



**Patient P203**



### Patient P205

