Supplementary material

Pharmacokinetics and exposure–response analysis of venetoclax+obinutuzumab in chronic lymphocytic leukemia: phase 1b study and phase 3 CLL14 trial

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## CLL14 Investigators and number of randomized patients by country

| Country         | Investigator(s)                  | Number of Patients |
|-----------------|----------------------------------|--------------------|
| Argentina       | Fantl                            | 1                  |
| Australia       | Harvey                           | 8                  |
|                  | Ho                               | 4                  |
|                  | Lai                              | 1                  |
|                  | Marlton                          | 1                  |
|                  | Opat                             | 10                 |
|                  | Schwarer                         | 8                  |
|                  | To                               | 6                  |
| Australia       | Wickham                          | 5                  |
| Austria         | Heintel                          | 2                  |
|                  | Jaeger                           | 1                  |
|                  | Nösslinger                       | 1                  |
|                  | Steurer                          | 1                  |
| Bulgaria        | Nenova                           | 3                  |
|                  | Nikolova-Yaprakova               | 5                  |
|                  | Sivcheva                         | 10                 |
| Brazil          | Russo                            | 6                  |
|                  | Santucci Alves da Silva          | 5                  |
|                  | Assouline                        | 1                  |
| Canada          | Owen                             | 1                  |
| Croatia         | Aurer                            | 8                  |
|                  | Ostojic                          | 4                  |
| Denmark         | Niemann                          | 9                  |
|                  | Poulsen                          | 7                  |
| Estonia         | Kaare                            | 1                  |
| France          | De Guibert                       | 2                  |
|                  | Dupuis                           | 3                  |
|                  | Le Dû                            | 10                 |
|                  | Leprêtre                         | 1                  |
| Germany         | Mahe                             | 3                  |
|                  | Molina                           | 3                  |
|                  | Ribrag                           | 1                  |
|                  | Sohn                             | 2                  |
| Germany         | Tournihac                        | 1                  |
| Germany         | Vilque                           | 3                  |
|                  | Zini                             | 3                  |
| Germany         | Bognner                          | 4                  |
| Germany         | Denzlinger                       | 1                  |
| Germany         | Dierks                           | 2                  |
| Germany         | Dreger                           | 4                  |
| Germany         | Duerig                           | 1                  |
| Germany         | Fischer-Von-Weikersthal          | 1                  |
| Germany         | Funck                            | 1                  |
| Germany         | Gaska                            | 2                  |
| Germany         | Graeven                          | 1                  |
| Germany         | Hallek                           | 1                  |
| Germany         | Hebart                           | 4                  |
| Germany         | Heilmeier                        | 1                  |
| Germany         | Jacobasch                        | 6                  |
| Germany         | Kiehl                            | 1                  |
| Germany         | Klaproth                         | 1                  |
| Germany         | Mannal                           | 2                  |
| Germany         | Pezzutto                          | 2                  |
| Germany         | Pezzutto                          | 1                  |
| Germany         | Schetelig                        | 3                  |
| Germany         | Schultheis                       | 4                  |
| Germany         | van Roye                         | 1                  |
| Germany         | Voehringer                       | 1                  |
| Germany         | Wendtner                         | 3                  |
| Germany         | Wirths                           | 5                  |
| Germany         | zur Hausen                       | 1                  |
| Italy           | Bassan                           | 1                  |
| Italy           | Coscia                           | 6                  |
| Italy           | Cuneo                            | 2                  |
| Italy           | Ghia                             | 1                  |
| Italy           | Laurenti                         | 1                  |
| Italy           | Liberati                         | 13                 |
| Italy           | Mannina                          | 2                  |
| Mexico          | Valdes-Cerda                     | 3                  |
| New Zealand     | Butler                           | 7                  |
| New Zealand     | Kilfoyle                         | 4                  |
| New Zealand     | McDiamid                         | 3                  |
| New Zealand     | Weinkove                         | 4                  |
| New Zealand     | Grosicki                         | 5                  |
| Poland          | Homenda                          | 3                  |
| Poland          | Robak                            | 6                  |
| Poland          | Wrobel                           | 2                  |
| Romania         | Burcoveanu                       | 1                  |
| Romania         | Oltean                           | 1                  |
| Romania         | Vasilica                         | 4                  |
| Russia          | Bakirov                          | 2                  |
| Russia          | Chagorova                        | 13                 |
| Russia          | Golubeva                         | 6                  |
| Russia          | Kuzmin                           | 2                  |
| Russia          | Maryin                           | 3                  |
| Russia          | Samoylova                        | 13                 |
| Russia          | Shatokhin                        | 1                  |
| Spain           | Andres                           | 1                  |
| Spain           | Carillo Cruz                     | 3                  |
| Spain           | Casado                           | 1                  |
| Spain           | De La Serna                      | 2                  |
| Spain           | Delgado                          | 1                  |
| Spain           | Goñi                             | 2                  |
| Spain           | Gonzales                         | 2                  |
| Spain           | Lopez                            | 2                  |
| Spain           | Loscertales                      | 7                  |
| Spain           | Machado                          | 1                  |
| Spain           | Terol                            | 2                  |
| Switzerland     | Andres                           | 1                  |
| Switzerland     | Gregor                           | 1                  |
| Switzerland     | Widmer                           | 1                  |
| UK              | Forconi                          | 1                  |
| UK              | Kallmeyer                        | 2                  |
| UK              | Kishore                          | 1                  |
| UK              | Rinaldi                          | 1                  |
| UK              | Scott                            | 2                  |
| USA             | Bessudo                          | 1                  |
| USA             | Bessudo                          | 1                  |
| USA             | Klueppelberg                     | 1                  |
| USA             | Kozloff                          | 2                  |
| USA             | Kipps                            | 4                  |
| USA             | Janakiraman                      | 4                  |
| USA             | Kipps                            | 1                  |
| USA             | Kozloff                          | 1                  |
Pinilla-Ibarz (USA; 12), Quick (USA; 2), Siddiqi (USA; 2).

**GP28331 Investigators and number of randomized patients by country**

Sharman (USA; 4), Flinn (USA; 11), Rogers (USA; 5), Kipps (USA; 13), Hillmen (UK; 5), Dyer (UK; 10), Gribben (UK; 5), Maris (USA; 8), Padmanabhan Iyer (USA; 5), Weirda (USA; 10), Furman (USA; 6).
| Site (country) | Name of ethics committee | Date of approval |
|---------------|--------------------------|-----------------|
| 277368 (DE)   | Ethik-Kommission der Albert-Ludwigs-Universität | 12 February 2014 |
| 273200 (AU)   | Bellberry Human Research Ethics Committee | 20 October 2014 |
| 276230        | Lehigh Valley Health Network IRB | 03 November 2014 |
| 273992, 275017| Health and Disability Ethics Committees | 03 November 2014 |
| & 275427      | Lehigh Valley Health Network IRB | 04 December 2014 |
| 275462 (US)   | Lehigh Valley Health Network IRB | 04 December 2014 |
| 273556, 273677, |                           |                 |
| 273678, 273679, |                           |                 |
| 273682, 273808, |                           |                 |
| 273809, 273827, | President: Jean-Etienne Bazin, Comité de Protection des | 15 December 2014 |
| 273832, 274762, | Personnes Sud-Est 6 |                 |
| 275015, 275040, |                           |                 |
| 275136, 275776 |                           |                 |
| & 276023 (FR) |                           |                 |
| 273846        |                           | 17 December 2014 |
| 273855 (DE)   | EK der Ärztekammer Nordrhein | 17 December 2014 |
| 273877 (DE)   | Ethik-Kommission der Medizinischen Fakultaet der L, Pettenkoferstr | 17 December 2014 |
| 273892 (DE)   | Ärztekammer des Saarlandes | 17 December 2014 |
| 273898 (DE)   | Ethik-Kommission der Landesärztekammer Bayern | 17 December 2014 |
| 273900 (DE)   | Ethik-Kommission der Universität Ulm | 17 December 2014 |
273915 (DE) Ethik-Kommission der Medizinischen Fakultät der L, Pettenkoferstr 17 December 2014
273921 (DE) Ethik-Kommission der Medizinischen Fakultät Heidelberg 17 December 2014
273985 (DE) Ethik-Kommission an der Medizinischen Fakultät der; Uniklinik Aachen 17 December 2014
274166 (DE) Ethik-Kommission an der Medizinischen Fakultät der 17 December 2014
274281 (DE) Ethik-Kommission der Medizinischen Fakultät 17 December 2014
274671 (DE) Ethikkommission bei der Landesaerztekammer Baden-W 17 December 2014
274672 (DE) Ethik-Kommission bei der Landesaerztekammer Rheinl 17 December 2014
275019 (DE) Ethikkommission der Universitaet Koeln 17 December 2014
274036 (ES) CEIC Parc de Salut Mar; IMIM- Hospital del Mar 15 January 2015
274037, 274039, 274042, 274047, 274050, 274150 & 275319 CEIC Hospital Vall D'Hebron 15 January 2015
274038 (ES) CEIC Hospital Virgen de la Salud 15 January 2015
274040 (ES) CEIC H Clinic i provincial de Barcelona 15 January 2015
274046 (ES) CEIC Hospital Universitario de Canarias 15 January 2015
274048 (ES) CEIC Hospital Universitario La Princesa 15 January 2015
274051 (ES) CEIC Hospital Clinico Universitario de Valencia 15 January 2015
275327 (ES) Hospital Virgen del Rocio, CEIC 15 January 2015
273171 (AU) Metro South HREC 16 January 2015
273414 21 January 2015
273417  Henry Ford Health System IRB  21 January 2015
274763  St. Joseph Health Institutional Review Board  21 January 2015
276026  Health Research Ethics Board of Alberta – Cancer  23 January 2015
273412  Nova Scotia Health Authority Research Ethics Board  26 January 2015
273973 (IT)  Comitato Etico delle Aziende Sanitarie dell’Umbria  28 January 2015
274667 (EE)  Tallinn Medical Research Ethics Committee  29 January 2015
278095  Health and Disability Ethics Committees  30 January 2015
275137  10 February 2015
273429, 273432,  
274165 & 276435  De Videnskabsetiske Komitéer for Region Hovedstade  11 February 2015
273436 (EST)  Tallinn Medical Research Ethics Committee  12 February 2015
273848 (DE)  Ethik-Kommission der Landesärztekammer Bayern  12 February 2015
273867  Ethik-Kommission der Universitaet Koeln  12 February 2015
273879 (DE)  Ethik-Kommission bei der Landesaertzekammer Baden-W  12 February 2015
274158 & 278876  Ethik-Kommission Berlin Landesamt für Gesundheit und (DE)  Soziales  12 February 2015
274295 (DE)  Ethik-Kommission der Medizinischen Fakultät der Ruhr-Universität Bochum  12 February 2015
274079, 275980,  
276858, 279119  NRES Committee East Midlands - Derby  16 February 2015
& 282797 (UK)  20 February 2015
273189  20 February 2015
273884 (DE)  EK Sächs  20 February 2015
| Identifier  | Institution                                                                 | Date               |
|------------|----------------------------------------------------------------------------|--------------------|
| 273972 (IT)| Comitato Etico Regione Liguria (Sezione 2)                                  | 23 February 2015   |
| 273232 (AT)| Ethikkommission der Medizinischen Fakultaet der Universitaet Wien und des AKH der Stadt Wien | 10 March 2015      |
| 273232, 273233 (AT) & 273234 (AT) | Ethikkommission der Stadt Wien gemäß KAG, AMG und MPG | 10 March 2015      |
| 273757     |                                                                           | 10 March 2015      |
| 275359 (AU)| Eastern Health Research and Ethics Committee                               | 11 March 2015      |
| 274054     | Ethikkommission Nordwest- und Zentralschweiz (EKNZ)                         | 17 March 2015      |
| 274021, 274022 (RO) & 275041 (RO) | Comisia Nationala de Bioetica a Medicamentului si a Dispozitivelor Medicale Comité de Ética Independiente en Investigaciones | 19 March 2015      |
| 275016 (AR)| Clinicas del Hospital Alemán (CEIHA)                                       | 20 March 2015      |
| 278018 (DE)| Ethik-Kommission der Fakultaet fuer Medizin der Tec                         | 26 March 2015      |
| 278489 (DE)| Ethik-Kommision der Ärztekammer Westfalen-Lippe                             | 26 March 2015      |
| 278490 (DE)| Ethik-Kommission bei der Landesaertzekammer Baden-W                         | 26 March 2015      |
| 278654 (DE)| Ethik-Kommission der Landesärztekammer Bayern                               | 26 March 2015      |
| 274031     |                                                                           | 27 March 2015      |
| 273969     |                                                                           | 30 March 2015      |
| 274030     |                                                                           | 31 March 2015      |
| 273967 (IT)| Comitato Etico Regione Liguria (Sezione 2)                                  | 01 April 2015      |
| 273342, 273344, 274738 & 275135 | Ethics Committee for Multicenter Trials                                     | 09 April 2015      |
| 279818     | Ingalls Memorial Hospital Institutional Review Board                        | 14 April 2015      |
| 276083     |                                                                           | 16 April 2015      |
| Code     | Institution/Committee                                                                 | Date          |
|----------|---------------------------------------------------------------------------------------|---------------|
| 273981 (CO) | Comité de Ética en Investigación, del Instituto Nacional de Cancerología               | 20 April 2015 |
| 275381 (AU) | South Western Sydney Local Health District                                               | 23 April 2015 |
| 275787     |                                                                                        | 23 April 2015 |
| 275977 (AU) | Human Research Ethics Committee                                                          | 23 April 2015 |
| 276843     |                                                                                        | 23 April 2015 |
| 276857     |                                                                                        | 23 April 2015 |
| 274033 (RU) | EC of Regional clinical hospital named after prof. S.V. Ochapovsky                     | 30 April 2015 |
| 276921     |                                                                                        | 14 May 2015   |
| 274034     | Komisja Bioetyczna przy Uniwersytecie medycznym                                        | 18 May 2015   |
| 274034     | Komisja Bioetyczna przy Uniwersytecie medycznym                                        | 28 May 2015   |
| 273865 (DE) | EK Sächs                                                                               | 10 July 2015  |
| 274253 (BR) | *X*Comissão Nacional de Ética em Pesquisa, Esplanada dos Ministérios - Ministério da Saúde | 10 July 2015  |
| 276027     | Komisja Bioetyczna przy Uniwersytecie medycznym                                        | 13 July 2015  |
| 276053     |                                                                                        | 17 July 2015  |
| 276229     |                                                                                        | 22 July 2015  |
| 279786 (CA) | Jewish General Hospital                                                                | 07 August 2015 |
| 275974 (BR) | *X*Comissão Nacional de Ética em Pesquisa, Esplanada dos Ministérios - Ministério da Saúde | 13 August 2015 |
| 273805 (BR) | *X*Comissão Nacional de Ética em Pesquisa, Esplanada dos Ministérios - Ministério da Saúde | 27 August 2015 |
| 274761 (BR) | *X*Comissão Nacional de Ética em Pesquisa, Esplanada dos Ministérios - Ministério da Saúde | 02 September 2015 |
| ID Number   | Institutional Review Board/Commission | Date Approved           |
|------------|----------------------------------------|-------------------------|
| 285835 (US)| Western Institutional Review Board     | 14 September 2015       |
| 273975     |                                        | 15 September 2015       |
| 284535 (US)| Chesapeake Research Review IRB         | 07 October 2015         |
| 276753     | Komisja Bioetyczna przy Uniwersytecie medycznym | 12 October 2015 |
| 273239 (BR)| *X*Comissão Nacional de Ética em Pesquisa, Esplanada dos Ministérios - Ministério da Saúde | 05 November 2015 |
| 284580     |                                        | 27 November 2015        |
| 274032     |                                        | 01 December 2015        |
| 283565 (US)| Lehigh Valley Health Network IRB       | 04 January 2016         |
| 274055 (CH)| Kantonale Ethikkommission Bern KEK     | 12 January 2016         |
| 276730     | Komisja Bioetyczna przy Uniwersytecie medycznym | 15 January 2016 |
### TABLE S2 GP28331 ethics committees

| Site (country)     | Name of ethics committee                                             | Date of approval |
|-------------------|-----------------------------------------------------------------------|------------------|
| 250074 (USA)      | IntegReview Ethical Review Board                                      | 20 July 2012     |
| 247962 (USA)      | Peace Health IRB; Institutional Review Board                         | 07 August 2012   |
| 247962 (USA)      | US Oncology, Inc Institutional Review Board                          | 07 August 2012   |
| 250742 (USA)      | Western Institutional Review Board                                   | 13 December 2012 |
| 264208 (USA)      | IntegReview Ethical Review Board                                      | 19 July 2013     |
| 250743 (USA)      | University of California, San Diego                                  | 01 August 2013   |
| 250752 (UK)       | NRES Committee Yorkshire and the Humber Leeds East                   | 14 October 2013  |
| 266221            |                                                                       | 12 November 2013 |
| 250753            |                                                                       | 26 November 2013 |
| 250754            |                                                                       | 06 December 2013 |
| 267576            |                                                                       | 07 August 2014   |
| 269434            |                                                                       | 14 October 2014  |
**TABLE S3** Summary of conditional individual predictions for model parameters and steady-state exposure, overall and by study

| Parameter, geometric mean (CV) | CLL14 n = 194 | GP28331 n = 80 | Total N = 274 |
|-------------------------------|---------------|----------------|--------------|
| F₁                            | 0.98 (0.14)   | 1.03 (0.18)    | 0.99 (0.15)  |
| CL/F (L/day)                  | 458 (0.31)    | 411 (0.34)     | 443 (0.32)   |
| V₂/F (L)                      | 183 (0.20)    | 180 (0.31)     | 182 (0.24)   |
| CL/F/F₁ (L/day)               | 469 (0.43)    | 397 (0.45)     | 447 (0.44)   |
| t₁/₂ (day)                    | 1.12 (0.10)   | 1.16 (0.15)    | 1.13 (0.12)  |
| AUCₜ (μg.ml⁻¹*day)            | 0.85 (0.43)   | 1.01 (0.45)    | 0.90 (0.44)  |
| Cₘₐₓₜ (μg.ml⁻¹)               | 1.18 (0.35)   | 1.37 (0.39)    | 1.23 (0.37)  |
| Cₜᵣᵤₒᵤₜ (μg.ml⁻¹)            | 0.43 (0.65)   | 0.53 (0.63)    | 0.46 (0.65)  |

AUCₜ, steady-state area under the concentration-time curve; CL, clearance; CL/F, apparent clearance; Cₘₐₓₜ, steady-state maximum drug concentration; Cₜᵣᵤₒᵤₜ, steady-state concentration at the end of a dosing interval; CV, coefficient of variation; F, bioavailability; F₁, relative bioavailability; t₁/₂, terminal half-life; V₂/F, apparent central volume.
TABLE S4 Summary of conditional predictions for model parameters and steady-state exposure, by patient population

| Parameter, geometric mean (CV) | Previously untreated unfit patients from CLL14 n = 194 | Previously untreated patients from GP28331 n = 32 | R/R patients from GP28331 n = 48 |
|--------------------------------|----------------------------------------------------------|--------------------------------------------------|----------------------------------|
| $F_1$                          | 0.98 (0.15)                                              | 1.00 (0.18)                                      | 1.03 (0.17)                      |
| CL/F (L/day)                   | 446 (0.32)                                               | 439 (0.35)                                       | 435 (0.29)                       |
| $V_2/F$ (L)                    | 183 (0.22)                                               | 190 (0.22)                                       | 172 (0.31)                       |
| CL/F/F1 (L/day)                | 454 (0.44)                                               | 436 (0.50)                                       | 424 (0.40)                       |
| $t_{1/2}$ (day)                | 1.13 (0.12)                                              | 1.14 (0.12)                                      | 1.13 (0.12)                      |
| AUC_{SS} ($\mu$g.ml$^{-1}$*day) | 0.88 (0.44)                                             | 0.92 (0.50)                                      | 0.94 (0.40)                      |
| $C_{\text{maxSS}}$ ($\mu$g.ml$^{-1}$) | 1.21 (0.37)                              | 1.25 (0.42)                                      | 1.31 (0.34)                      |
| $C_{\text{troughSS}}$ ($\mu$g.ml$^{-1}$) | 0.45 (0.65)                              | 0.48 (0.74)                                      | 0.48 (0.58)                      |

AUC_{SS}, steady-state area under the concentration-time curve; CL, clearance; CL/F, apparent clearance; $C_{\text{maxSS}}$, steady-state maximum drug concentration; $C_{\text{troughSS}}$, steady-state concentration at the end of a dosing interval; CV, coefficient of variation; F, bioavailability; $F_1$, relative bioavailability; R/R, relapsed or refractory; $t_{1/2}$, terminal half-life; $V_2/F$, apparent central volume.
| Parameter, geometric mean (CV) | Stage A $n = 45$ | Stage B $n = 70$ | Stage C $n = 79$ |
|-------------------------------|-----------------|-----------------|-----------------|
| $F_1$                         | 1.03 (0.18)     | 0.99 (0.13)     | 0.99 (0.15)     |
| CL/F (L/day)                  | 411 (0.34)      | 444 (0.31)      | 449 (0.34)      |
| $V_2/F$ (L)                   | 180 (0.31)      | 175 (0.21)      | 189 (0.17)      |
| CL/F/F$_1$                    | 397 (0.45)      | 450 (0.42)      | 455 (0.48)      |
| $t_{1/2}$ (day)               | 1.16 (0.15)     | 1.12 (0.09)     | 1.13 (0.13)     |
| $AUC_{SS}$                    | 1.01 (0.45)     | 0.89 (0.42)     | 0.88 (0.48)     |
| (μg.ml$^{-1}$*day)            |                 |                 |                 |
| $C_{maxSS}$ (μg.ml$^{-1}$)   | 1.37 (0.39)     | 1.23 (0.33)     | 1.20 (0.40)     |
| $C_{troughSS}$ (μg.ml$^{-1}$) | 0.53 (0.63)     | 0.45 (0.68)     | 0.46 (0.69)     |

$AUC_{SS}$, steady-state area under the concentration-time curve; CL, clearance; CL/F, apparent clearance; $C_{maxSS}$, steady-state maximum drug concentration; $C_{troughSS}$, steady-state concentration at the end of a dosing interval; CV, coefficient of variation; F, bioavailability; $F_1$, relative bioavailability; $t_{1/2}$, terminal half-life; $V_2/F$, apparent central volume
### TABLE S6
Assessment of exposure ($C_{\text{meanSS}}$) as a predictor of PFS

| Model                        | Parameter                  | $\beta$   | SE  | RSE (%) | p value | OF     | $\Delta$ OF |
|------------------------------|----------------------------|-----------|-----|---------|---------|--------|-------------|
| **Investigator-assessed data** |                            |           |     |         |         |        |             |
| $C_{\text{meanSS,nominal}}$  | $C_{\text{mean}}$ (μg.ml$^{-1}$) | $-0.5231$ | $0.542$ | 103.52  | $0.33$  | 268.19 | $-1.04278$ |
| Categorical exposure: tertiles of $C_{\text{meanSS,nominal}}$ | Tertile 2 vs 1 | $0.5696$  | $0.435$  | 76.29   | $0.19$  | 265.96 | $-5.27278$ |
|                             | Tertile 3 vs 1             | $-0.5625$ | $0.558$  | 99.21   | $0.31$  |        |             |
| **IRC-assessed data**        |                            |           |     |         |         |        |             |
| $C_{\text{meanSS,nominal}}$  | $C_{\text{mean}}$ (μg.ml$^{-1}$) | $-0.6071$ | $0.563$  | 92.69   | $0.28$  | 254.4  | $-1.32062$ |
| Categorical exposure: tertiles of $C_{\text{meanSS,nominal}}$ | Tertile 2 vs 1 | $0.4499$  | $0.441$  | 98.07   | $0.31$  | 251.71 | $-4.01062$ |
|                             | Tertile 3 vs 1             | $-0.5644$ | $0.558$  | 98.94   | $0.31$  |        |             |

$C_{\text{meanSS,nominal}}$, nominal exposure at steady state; IRC, independent review committee; OF, objective function value; $\Delta$ OF, change of the objective function value relative to the null model that does not include any parameters; PFS, progression-free survival; RSE, relative standard error of $\beta$ estimate (%); SE, standard error of $\beta$ estimate.
FIGURE 1 Goodness of fit of the final model for CLL14 study data

DV, observed concentrations; PRED, population predictions of the model; IPRED, individual predictions of the model; CWRES, conditional weighted residuals; TIME, time after the first dose. The gray solid $y = x$ or $y = 0$ lines are included for reference. The bold red lines are the LOWESS (local weighted scatterplot smoothing) trend lines. Plots of CWRES versus time after dose are shown for the intervals of 10 days and 1.2 days, to magnify the time interval of interest.
FIGURE 2 Goodness of fit of the final model for GP28331 study data

DV, observed concentrations; PRED, population predictions of the model; IPRED, individual predictions of the model; CWRES, conditional weighted residuals; TIME, time after the first dose.

The gray solid $y = x$ or $y = 0$ lines are included for reference. The bold red lines are the LOWESS (local weighted scatterplot smoothing) trend lines. Plots of CWRES versus time after dose are shown for the intervals of 10 days and 1.2 days, to magnify the time interval of interest.
FIGURE 3 NPDE plots for CLL14 study data

NPDE, normalized prediction distribution errors

Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at $y = 0$ correspond to median, and dashed lines show the 10th and 90th percentiles. Percentages of points below the 10th percentile and above the 50th and 90th percentiles are reported. Red lines show the LOWESS (local weighted scatterplot smoothing) trend lines.
**FIGURE 4** NPDE plots for GP28331 study data

NPDE, normalized prediction distribution errors

Circles correspond to NPDE of observations in the distribution of 500 simulated values. Lines at \( y = 0 \) correspond to median, and dashed lines show the 10\(^{\text{th}}\) and 90\(^{\text{th}}\) percentiles. Percentages of points below the 10\(^{\text{th}}\) percentile and above the 50\(^{\text{th}}\) and 90\(^{\text{th}}\) percentiles are reported. Red lines show the LOWESS (local weighted scatterplot smoothing) trend lines.
**FIGURE 5** Kaplan-Meier analysis of time to progression (IRC-assessed data). Exposure groups correspond to quartiles of $C_{\text{meanSS,nominal}}$

![Kaplan-Meier of PFS by Exposure](image)

| Subjects at risk: | 1st    | 2nd    | 3rd    | 4th    |
|------------------|--------|--------|--------|--------|
| 1st:             | 51     | 51     | 50     | 48     | 40     | 6      | 0      |
| 2nd:             | 50     | 49     | 49     | 45     | 36     | 4      | 0      |
| 3rd:             | 51     | 44     | 43     | 39     | 34     | 6      | 0      |
| 4th:             | 51     | 48     | 48     | 47     | 37     | 7      | 0      |

$C_{\text{meanSS,nominal}}$, nominal exposure at steady state; IRC, independent review committee; PFS, progression-free survival