Appendix 1. Prediction of mortality

The models estimate individual patient mortality by adjusting background mortality hazards derived from the US CFFPR 1992 to 2011 birth cohorts to account for individual patient characteristics that predict survival based on a Cox proportional hazards (CPH) model published by Liou et al. (21). The projected mortality hazard for patients with CF estimated in this model is also capped by the sex-specific general US population mortality hazard at each age.

The US CFF provided the accompanying life table output for the Kaplan–Meier survival curves of five birth cohorts published in the 2011 US CFFPR (cohort groups: 1987 to 1991, 1992 to 1996, 1997 to 2001, 2002 to 2006, and 2007 to 2011). The life table output included number of deaths as well as numbers at risk at yearly intervals. These were processed to generate virtual patient-level data by assigning death or alive (i.e. censored) status at each age based on the available counts for each cohort.

The data were analyzed to test various parametric distributions; these included the exponential, Weibull, Gompertz, log-normal, gamma, and log-logistic. The optimal parametric fit was selected based on statistical fit (Akaike Information Criterion and the Bayesian Information Criterion, closeness of fit in comparisons of observed and predicted curves), as well as based on the clinical plausibility of fits (based on median survival times, and shape of projected curves).

Data from each of the birth cohort groups were first analyzed separately to assess the possibility of accurate fitting in the most recent cohorts (e.g. 2007 to 2011), as these are more reflective of current survival expectations. Follow-up in these groups was very short with curves dropping by a few percent only, which led to projections of implausibly long survival. Thus, the birth cohorts were grouped in order to overcome this issue. The final analyses were based on survival data from the 1992 to 2011 cohorts (Appendix 1 Figure 1).
A Gompertz fit to the 1992 to 2011 birth cohorts produced the most plausible projection, with the curve reaching 0% near 65 years of age, and a predicted median of 39.7 years (Appendix 1 Figure 1, Appendix 1 Table 1). The survival of birth cohorts for 2012 and after were not updated in the US CFFPR reports published after 2011; therefore, they were not included in the fitting exercise.

Appendix 1 Figure 1. Kaplan-Meier curve and parametric fits to the US CFF population (all genotypes): combined birth cohort 1992 to 2011

The Gompertz survival function used in the model is shown below:

\[ S(t) = e^{(1-e^{\gamma t})\lambda/\gamma} \]
Appendix 1 Table 1. Parameters for Gompertz distribution used to derive CF survival projections based on US CFFPR population (all genotypes): birth cohort 1992 to 2011

| Parameter | Value |
|-----------|-------|
| \( \lambda \) | -6.7273 |
| \( \gamma \) | 0.1033 |

The survival projections in the model are adjusted to reflect the characteristics of the simulated patients. For patients receiving lumacaftor/ivacaftor, the projections are further adjusted to account for the assumed treatment benefit gained by adding lumacaftor/ivacaftor to SC. Liou et al. developed the CPH model based on data collected from 1993 to 1997 by the US CFFPR on 11,630 individuals — the following nine characteristics of patients with CF were found to predict survival: age, ppFEV\(_1\), sex, weight-for-age z-score, pancreatic sufficiency, diabetes, \( S. \) aureus infection, \( B. \) cepacia infection, and number of acute exacerbations per year (21). Reference values for each of these characteristics were used to make the adjustment from the US CFFPR to an individual patient in the model at baseline. Covariates included in the Liou model and the corresponding coefficients, as well as the reference values used in the model, are presented in Appendix 1 Table 2.
# Appendix 1 Table 2. Cox proportional hazards model coefficients and reference values

| Covariate                                           | Coefficient* | Mean Characteristics of Reference Population |
|-----------------------------------------------------|--------------|---------------------------------------------|
|                                                     | β            | SE              |                                            |
| Age (per year)                                      | 0.011        | 0.0049          | 19.8†                                      |
| Sex (female = 1)                                    | 0.15         | 0.074           | 0.48                                       |
| ppFEV\(_1\) (per %)                                 | -0.042       | 0.0025          | 77.1                                       |
| Weight-for-age z-score                              | -0.28        | 0.041           | -0.85‡                                     |
| Pancreatic sufficiency (yes = 1)                    | -0.14        | 0.23            | 0.126                                      |
| Diabetes mellitus (yes = 1)                         | 0.44         | 0.098           | 0.19                                       |
| S. aureus (yes = 1)                                 | -0.25        | 0.09            | 0.68                                       |
| B. cepacia (yes = 1)                                | 1.41         | 0.19            | 0.03                                       |
| Annual number of acute exacerbations (maximum 5)     | 0.35         | 0.024           | 0.7                                        |
| PEx B. cepacia                                      | -0.28        | 0.06            | 0.0286§                                    |

Mean estimates obtained from US CFFPR 2011, except where indicated.

* Unless specified, coefficients for each covariate are unitless.

† Data not available from the US CFFPR 2011. Data reported in US CFFPR 2012 is used as proxy.

‡ Liou et al. 2001 (21).

§ Assumed equal to mean B. cepacia mean acute exacerbations.

* B. cepacia, Burkholderia cepacia; PEx, pulmonary exacerbation; ppFEV\(_1\), percentage of predicted forced expiratory volume in 1 second; S. aureus, Staphylococcus aureus; SE, standard error.
While the CPH model has not been updated since its publication, Liou et al. presented an updated analysis in 2015 of the logistic regression that was originally published alongside the CPH model in 2001 (21). The updated logistic regression used US CFFPR data from 1993 to 2010. This analysis concluded that while there were some slight changes to coefficients, the factors predicting mortality in patients with CF have remained stable. These results support continued use of the 2001 CPH model in these simulations.

The probability of death at each cycle in the survival model ($p$) is calculated using the following formula:

$$ p = 1 - \exp(-h \times t) $$

Where $h$ is the annual mortality hazard calculated at that cycle and $t$ is the cycle length (in years). Random numbers are used to determine in which cycle an individual patient would die. After death, the patient exits the model and the next patient is simulated through the model.

References to Appendix 1

21. Liou TG, Adler FR, Fitzsimmons SC, Cahill BC, Hibbs JR, Marshall BC. Predictive 5-year survivorship model of cystic fibrosis. Am J Epidemiol. 2001;153:345-52.
Appendix 2. Assumptions for clinical inputs

Percent predicted forced expiratory volume in 1 second

Over the first 24 weeks after lumacaftor/ivacaftor initiation, an increase in ppFEV\textsubscript{1} was assumed, based on the placebo-controlled treatment effects from the relevant clinical trials (10,18). Patients initiating lumacaftor/ivacaftor + SC at ages of 6 to 11 years were assumed to experience an acute increase of 2.4 percentage points in ppFEV\textsubscript{1} by Week 24 of the simulation. Whereas, patients initiating at age ≥12 years were assumed to experience an acute increase of 2.8 percentage points in in ppFEV\textsubscript{1} over the first 24 weeks of the model, based on the placebo-controlled changes observed at the average of Weeks 16 and 24 in TRAFFIC/TRANSPORT (primary clinical endpoint); simulated patients therefore receive an acute increase in ppFEV\textsubscript{1} by Week 16 and remain at that level until Week 24 of the simulation. Patients receiving SC alone were assumed to have no change in ppFEV\textsubscript{1} over the initial 24 weeks, since placebo-adjusted treatment effects were used for patients receiving lumacaftor/ivacaftor + SC.

It is well-documented that lung function declines over time in patients with CF (19,22,23,46). After 24 weeks, the model assumed age-dependent annual ppFEV\textsubscript{1} decline for the remainder of the simulation, based on the findings from Konstan et al. 2007 (22) and 2012 (23). Patients receiving lumacaftor/ivacaftor + SC were assumed to have a reduced rate of ppFEV\textsubscript{1} decline relative to SC alone (13). Based on findings from a matched analysis of data from TRAFFIC/TRANSPORT and PROGRESS studies comparing patients on lumacaftor/ivacaftor to a matched control cohort from the US CFFPR (13), the model assumed that while a patient was receiving lumacaftor/ivacaftor + SC, they had a 42% slower annual rate of decline in ppFEV\textsubscript{1}.

PEx rate

Occurrence of PEx per patient in each model cycle was predicted contingent on patient ppFEV\textsubscript{1} and age from a relationship derived from the 2004 US CFFPR, based on a
publication by Goss et al. 2007 (32). PEx rates were found to increase with lower ppFEV₁. The data reported were fitted to an exponential regression function, to provide a continuous relationship between the PEx rates and ppFEV₁ (24).

\[ PEx \ rate = a \times \exp(-b \times ppFEV₁) \]

Two equations were applied: for patients aged < 18 years \((a = 8.594, b = 0.035)\), and \(\geq 18\) years \((a = 3.789, b = 0.026)\). Since the PEx events tracked in this data source were likely those that were treated with intravenous antibiotics and/or hospitalization, it is this subset of PEx that is tracked in the model.

For patients aged 6 to 11 years, no treatment effect of lumacaftor/ivacaftor + SC was assumed on PEx, as the 809-109 study was not powered to detect a difference in PEx rate. For patients aged \(\geq 12\) years, lumacaftor/ivacaftor + SC treatment was assumed to reduce the rate by 56%, the observed treatment effect on the rate of PExs treated with intravenous antibiotics from TRAFFIC/TRANSPORT study (10).

**Weight-for-age z-score**

During the first 2 years of the simulation, patients on lumacaftor/ivacaftor + SC were assumed to experience a constant weight-for-age z-score increase of 0.033 per year based on the findings from the registry-matched analysis by Konstan et al. (13). Patients on SC alone declined by 0.030 per year for the first two years after baseline (13). Weight-for-age z-score was updated during the first 2 years of treatment and was subsequently assumed to remain constant over time.

**Lung transplantation**

International guidelines suggest that patients with CF and a ppFEV₁ of < 30% should be evaluated for lung transplantation (31). Thus, in the model, patients were assumed to be eligible to receive a lung transplant when ppFEV₁ fell below 30%. The percentage of eligible patients who went on to receive a transplant was estimated to be 26.8%, based on data from
the 2015 US CFFPR report (2), this was implemented in the model as a one-time chance (26.8% risk) of receiving a lung transplant once ppFEV\textsubscript{1} fell below 30%.

**Lumacaftor/ivacaftor discontinuation**

Discontinuation rates for Weeks 1 to 24 of the simulation were derived from discontinuation data from either (i) TRAFFIC/TRANSPORT for patients who were aged ≥ 12 years at baseline, or (ii) the 809-109 study for patients aged 6 to 11 years at baseline. The discontinuation rate for Weeks 25 to 96 was based on the discontinuation from the first 72 weeks of the PROGRESS study (13). While PROGRESS only included patients aged ≥ 12 years who completed TRAFFIC/TRANSPORT, the model assumed these data were applicable for patients aged ≥ 6 years in the absence of longer-term lumacaftor/ivacaftor discontinuation data for patients aged 6 to 11 years. Patients who discontinued lumacaftor/ivacaftor during the first 24 weeks of the model were assumed to retain the acute increase in ppFEV\textsubscript{1}, as the ppFEV\textsubscript{1} treatment effect was derived from an intent-to-treat analysis and so included patients who discontinued. In contrast, for patients who discontinued lumacaftor/ivacaftor between in Weeks 25 to 96, the acute ppFEV\textsubscript{1} increase was removed in the cycle in which the patient discontinues. The model assumed no discontinuation of lumacaftor/ivacaftor after 96 weeks. Upon discontinuation of lumacaftor/ivacaftor, a patient was assumed to transition to SC alone.

**References to Appendix 2**

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Appendix 3. Parameter inputs in deterministic sensitivity analysis (DSA)

Appendix 3 Figure 1. Lower and upper bound for each model parameter in DSA

| Parameter                                                                 | INPUTS                                                                 |
|---------------------------------------------------------------------------|------------------------------------------------------------------------|
|                                                                           | Base case | Lower bound | Upper bound | Bounds source                                      |
| Long-term reduction in rate of ppFEV₁ decline with LUM/IVA+SC (all ages) |           |             |             | 95% CI (Konstan 2017, VXR-HQ-88-00035) (13)         |
| LUM/IVA+SC PEx rate ratio for patients ≥ 12 years                         | 0.44      | 0.33        | 0.60        | 95 % CI (Wainwright 2010) (10)                      |
| LUM/IVA discontinuation rates                                            | Multiple  | 20% lower   | 20% greater | Assumption                                         |
| Change in ppFEV₁ by Week 16 for LUM/IVA+SC patients ≥ 12 years           | 2.8       | 1.8         | 3.8         | 95% CI (Wainwright 2010) (10)                       |
| Change in ppFEV₁ by Week 24 for LUM/IVA+SC patients 6 to 11 years        | 2.4       | 0.4         | 4.4         | 95% CI (Ratjen 2017) (18)                          |
| ppFEV₁ threshold for lung transplant                                     | 30        | 20          | 40          | Assumption                                         |
| Multiplier for annual PEx rate (parameter a of Goss equation), patients ≥ 18 years | 3.789     | 3.031       | 4.547       | Assumption (20% lower/higher)                      |
| Age-dependent ppFEV₁ annual rates of decline after 24 weeks             | Multiple  | 20% lower   | 20% greater | Assumption (20% lower/higher)                      |
| Post lung transplant mortality, years ≥ 2 after transplant               | 5.70%     | 4.56%       | 6.84%       | Assumption (20% lower/higher)                      |
| Change in weight-for-age z-score over 2 years for LUM/IVA + SC patients | 0.066     | 0.012       | 0.122       | 95% CI (Konstan 2017) (13)                         |
| Prevalence of S. aureus at baseline                                      | 70.60%    | 56.48%      | 84.72%      | Assumption (20% lower/higher)                      |
| Post lung-transplant mortality, year 1 after transplant                  | 15.18%    | 12.14%      | 18.22%      | Assumption (20% lower/higher)                      |
| Percentage of eligible patients receiving lung transplantation           | 26.81%    | 21.45%      | 32.17%      | Assumption (20% lower/higher)                      |
| Change in weight-for-age z-score over 2 years for SC patients           | -0.06     | -0.09       | -0.03       | 95% CI (Konstan 2017) (13)                         |
| Multiplier for annual PEx rate (parameter a of Goss equation), patients <18 years | 8.594     | 6.875       | 10.313      | Assumption (20% lower/higher)                      |
| Minimum ppFEV₁                                                           | 15        | 12          | 18          | Assumption (20% lower/higher)                      |
| Prevalence of B. cepacia at baseline                                     | 2.60%     | 2.08%       | 3.12%       | Assumption (20% lower/higher)                      |
| Prevalence of diabetes at baseline                                       | Multiple  | 20% lower   | 20% greater | Assumption (20% lower/higher)                      |
Appendix 3 Figure 2. DSA tornado diagram: lumacaftor/ivacaftor + SC vs. SC alone

Long-term reduction in rate of ppFEV1 decline with lumacaftor/ivacaftor (all ages)
Age-dependent ppFEV1 annual rates of decline after 24 weeks
Lumacaftor/ivacaftor PEx rate ratio for patients age ≥ 12 years
Lumacaftor/ivacaftor discontinuation rates
Change in ppFEV1 by week 16 for lumacaftor/ivacaftor patients age ≥ 12 years
Change in ppFEV1 by week 24 for lumacaftor/ivacaftor patients age 6 to 11 years
ppFEV1 threshold for lung transplant
Multiplier for annual PEx rate (parameter a of Goss equation), patients age ≥ 18 years
Post lung transplant mortality, years ≥ 2+ after transplant
Change in weight-for-age z-score over 2 years for lumacaftor/ivacaftor patients
Prevalence of S. aureus at baseline
Post lung-transplant mortality, year 1 after transplant

Abbreviations: ppFEV1, percent-predicted forced expiratory volume in 1 second; PEx, pulmonary exacerbation.

References to Appendix 3

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Appendix 4. Probabilistic sensitivity analysis (PSA)

A PSA was conducted to account for multivariate and stochastic uncertainty in the model. The PSA tests effect of statistical uncertainty of model parameters on model outcomes. The uncertainty in the individual parameters was characterized using probability distributions and analyzed using Monte Carlo simulation (1,000 replications). In the PSA, the uncertainties around parameters were estimated as shown in Appendix 4 Table 1. Output from the PSA was used to derive 95% credible intervals on the point estimates.

Appendix 4 Table 1. PSA Assumptions

| Parameter                                                                 | Distribution                        | Mean  | Standard error | Source                                                |
|---------------------------------------------------------------------------|-------------------------------------|-------|----------------|-------------------------------------------------------|
| Change in ppFEV\(_1\) by Week 16 for LUM/IVA+SC patients ≥ 12 years       | Normal, bounded by 0                | 2.80  | 0.52           | 95% CI (Ratjen 2017) (18)                             |
| Change in ppFEV\(_1\) by Week 24 for LUM/IVA+SC patients 6 to 11 years    | Normal, bounded by 0                | 2.40  | 1.00           | 95% CI (Wainwright 2010) (10)                         |
| Change in weight-for-age z-score over 2 years for LUM/IVA+SC patients     | Normal, bounded by 0                | 0.066 | 0.028          | 95% CI (Konstan 2017) (13)                            |
| Change in weight-for-age z-score over 2 years for SC patients             | Normal, bounded by 0                | -0.060| 0.015          | 95% CI (Konstan 2017) (13)                            |
| Age-dependent ppFEV\(_1\) rates of decline after 24 weeks for SC 6–8 years| Normal, bounded by 0                | -1.12 | 0.22           | Assumed 20% of mean                                  |
| Age-dependent ppFEV\(_1\) rates of decline after 24 weeks for SC 9–12 years| Normal, bounded by 0                | -2.39 | 0.48           | Assumed 20% of mean                                  |
| Age-dependent ppFEV\(_1\) rates of decline after 24 weeks for SC 13–17 years| Normal, bounded by 0                | -2.34 | 0.47           | Assumed 20% of mean                                  |
| Age-dependent ppFEV\(_1\) rates of decline after 24 weeks for SC 18–24 years| Normal, bounded by 0                | -1.92 | 0.38           | Assumed 20% of mean                                  |
| Age-dependent ppFEV\(_1\) rates of decline after 24 weeks for SC 25+ years| Normal, bounded by 0                | -1.45 | 0.29           | Assumed 20% of mean                                  |
| Long-term reduction in rate of ppFEV\(_1\) decline with LUM/IVA+SC (all ages)| Beta, bounded by 0                  | 42.0% | 0.112          | 95% CI (Konstan 2017, VXR-HQ-88-00035) (13)           |
| LUM/IVA+SC PEx rate ratio for patients ≥ 12 years                          | Log-normal, bounded by 0            | 0.440 | 0.152          | 95% CI (Wainwright 2010) (10)                         |
| Multiplier for annual PEx rate (parameter a of Goss equation), patients ≥ 18 years| Normal, bounded by 0                | 8.594 | 1.719          | Assumed 20% of mean                                  |
| Multiplier for annual PEx rate (parameter a of Goss equation), patients ≥ 18 years| Normal, bounded by 0                | 3.789 | 0.758          | Assumed 20% of mean                                  |
LUM/IVA, lumacaftor and ivacaftor; ppFEV₁, percent-predicted forced expiratory volume in 1 second; PEx, pulmonary exacerbation; SC, standard care.

The empirical distribution of mean residual life years and median predicted survival results from the PSA (Appendix 4 Figure 1 and Appendix 4 Figure 2, respectively) delineate that treatment with LUM/IVA + SC yields additional survival benefits across all PSA replications, relative to SC.

Appendix 4 Figure 1A. PSA Histogram of Incremental Residual Life Years (Base Case)
Appendix 4 Figure 1B. PSA Histogram of Incremental Median Predicted Survival (Base Case)
Appendix 4 Figure 2A. PSA Histogram of Incremental Residual Life Years (100% Persistence)
Appendix 4 Figure 2B. PSA Histogram of Incremental Median Predicted Survival

(100% Persistence)
Appendix 5. Model validation

To validate the input cohort and natural disease history assumptions in the model, a cohort with baseline characteristics that resembled the population used to derive the registry reference curve detailed in Appendix 1 (i.e. patients with CF of all ages and all genotypes in the US CFFPR) was simulated. It would be expected that simulating such a cohort through the SC of the model would produce a survival curve similar to the reference curve derived from registry data using parametric survival analysis. A registry-matched cohort was generated with mean characteristics similar to those of the 2011 US CFFPR population. The model’s projected survival of this simulated cohort was compared to the curve fitted to the registry population. To create this validation cohort, it was necessary to deduce baseline risk profiles that collectively yielded the average profile. As such, a perfect match of the simulation to the registry cannot be expected. Nevertheless, the model output is a good fit to the registry survival curve, as shown in Appendix 5 Figure 1.

Appendix 5 Figure 1. Validation of simulated cohort survival