CLADRIBINE TABLETS

DOSING RULES

Simulation analysis of absolute lymphocytes counts (ALC) and relapse rate (RR) following cladribine treatment rules in subjects with relapsing-remitting multiple sclerosis (RRMS)

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Outline

1. Objective

2. Clinical Trial Simulation workflow

3. Evaluation of alternative treatment rules

4. Conclusions

Cladribine treatment rules | June 7, 2017
Cladribine exerts sustained effects in RRMS by selective depletion of lymphocytes.

A minority of patients develop Grade 3/4 lymphopenia at any time (25%, CLARITY study). Most of these occurred in patients receiving cladribine treatment when their absolute lymphocyte counts (ALC) were at Grade 2 or worse.

**Proposed Risk Minimization: treatment guidelines**

- Cladribine 3.5 mg/kg at Month 1 and 2 of Year 1 and 2
- Year 1
  - 1
  - 2
- Year 2
  - 3
  - 4

- Weekly treatment
- Postponement

**Alternative rules:**
*Treatment postponements during Year 2 allowed in blocks of 1/2/3 months in patients with lymphopenia Grade 2-4 or 3-4.*
- If, after three postponements, a patient’s ALC value had not recovered to Grade 0/1, the treatment would stop.
Assessing the impact of treatment guidelines on the occurrence of relapses requires clinical trial simulations

- Obtain projections for **Relapse Rate** (RR) and the **Absolute Lymphocyte Counts** (ALC) dynamics by accounting for treatment delays or cancellations in patients presenting lymphopenia of Grade 2-4.

- Investigate the **impact of postponement of dosing or cancellation of treatment** with cladribine tablets on the probability of being relapse free over time in RRMS subjects.
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Satisfactory model of ALC vs. time and exposure

Prior ALC modeling information

Population PD modeling approach*

Indirect response model with cladribine stimulating the loss function (lymphocyte perish rate) through an $E_{\text{max}}$ drug-effect relationship to cladribine exposure

Good description of ALC dynamics following treatment with cladribine according to different schedules

Good capabilities in predicting different CTCAE grades of lymphopenia

Credits: Pharmacometrics group at Uppsala University

*CLARITY, CLARITY Extension and Oracle Studies
Modelling shows that 3.5 mg/kg dose is already at the shoulder of exposure-efficacy curve

Prior RR modeling information

**Population Repeated Time-to-Event (RTTE) model of qualifying relapses***

- Weibull hazard function with decreasing hazard over time
- **Inhibitory Emax** dose-effect relationship on hazard, using cumulative dose with implemented decay as effect driver

\[ h(t) = h_0(t) \times \left(1 - \frac{E_{\text{max}} \times \text{Exp}(t)}{D_{50} + \text{Exp}(t)}\right) \]

**Effect compartment exposure,** linking the short systemic exposure to the long-lasting effect

- Baseline hazard \(h_0\) given by: \(h_0(t) = \lambda \gamma(t)^{\gamma-1}\)
- Dose adjusted for \(CR_{CL}(t)\) centered on population median
- IIV and covariate EXNB (number of exacerbation prior to study entry) on \(\lambda\)

Good description of the time to occurrence (and re-occurrence) of qualifying relapses
Showed that the **3.5 mg/kg cumulative dose is truly appropriated** in reducing the risk of relapses

*CLARITY, CLARITY Extension and Oracle Studies*
Simulation strategy relies on a complex workflow

1. **Exploratory and Graphical Analysis**
   - ALC model
   - RTTE model for RR
   - Correlation?

2. **Virtual subjects generation**
   - Covariate resampling

3. **Clinical Trial Simulation to reproduce CLARITY scenario**
   - ALC distributions at Week 49
   - Relapse-free survival (%)

4. **Simulation of alternative treatment rules**
   - Year 1
     - 1 2
   - Year 2
     - 3 4
     - Postponement
   - Any impact on Relapse-free survival (%)?

**Simulx** was employed for simulations, with models encoded in MLXTRAN

http://lixoft.com/products/simulx/
CLARITY was considered as the clinical trial to be simulated

**Covariate and execution models**

- **Target population**
- **Covariate Distribution Model**
- **Exclusion Criteria**
- **Trial Execution Model**
- **Replication of the Study**

- **Subjects with RRMS** from the Phase III cladribine trial (*CLARITY*)
- **Sampling** of model covariates from observed distributions by accounting for their relationships (covariance), and assignment to each virtual subject
- Covariates considered as constant (no time-varying)
- Patients with **baseline lymphopenia** Grade 1-4 (as part of the risk minimization plan)
- **Cladribine** total cumulative dose of **3.5 mg/kg** over 4 or 5 days at **Month 1 and 2 of Year 1 and 2**
- No randomization rules or deviations from the protocol
- Initial virtual population of **5000 subjects**
- Study **size increase** by blocks of 2000 subjects until model **output comparable** with observations

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Generating individual virtual subjects representative of subjects in CLARITY study

Input-Output Model

Individual model parameters

Covariate Model

Physiologically reasonable covariate distributions

Decision tree for virtual population generation

Assessment of correlations among saturated random effects of the two models: $r^2(\beta_{\text{CL}, \text{Subject}}) \neq 0.99$

More than one fixed-effect parameter $\gamma_{\text{CL}, \text{Subject}}$ and $\gamma_{\text{SG}}$ with $R^2 > 0.99$

No

Yes

Model simulations with
$\gamma_{\text{CL}, \text{Subject}}$ sampled from MVN($\mu_{\gamma_{\text{CL}, \text{Subject}}}$, $\Sigma_{\gamma_{\text{CL}, \text{Subject}}}$)
$\gamma_{\text{SG}}$ sampled from MVN($\mu_{\gamma_{\text{SG}}}$, $\Sigma_{\gamma_{\text{SG}}}$)
$X$ times resampling

Model simulations with
$\gamma_{\text{CL}, \text{Subject}}$ sampled from MVN($\mu_{\gamma_{\text{CL}, \text{Subject}}}$, $\Sigma_{\gamma_{\text{CL}, \text{Subject}}}$)
$\gamma_{\text{SG}}$ sampled from MVN($\mu_{\gamma_{\text{SG}}}$, $\Sigma_{\gamma_{\text{SG}}}$)
$X$ times resampling

Number of exacerbation prior to study entry

Female (N=3400)

Male (N=1600)
Using 5000 virtual patients, the simulation workflow could be validated, reproducing CLARITY scenario

**ALC model simulations**
Reproducing subject distributions within lymphopenia grades

**RTTE model simulations**
Reproducing proportions of subject not experiencing 1-6 relapses

Virtual patients treated with cladribine total cumulative dose of 3.5 mg/kg according to the CLARITY trial protocol
The simulation allowed to identify those virtual patients requiring postponement, based on their ALC observed at the end of Year 1

- Regardless of block definition (1, 2 or 3 months) only 3% of virtual subjects required two or more treatment postponements

92% of subjects treated without postponements

About 5% of subjects required only the first postponement

Less than 1% of subjects required treatment cancellation during Year 2

Alternative scenario 2:
Treatment postponements during Year 2 allowed in blocks of two months in patients with lymphopenia Grade 2-4

- Of those who qualified for postponements (lymphopenia Grade 2-4), less Grade 3-4 lymphopenia was observed at anytime during Year 2 when applying the postponement rules.
The dosing algorithms had no impact on the probability of having a relapse over the 2-year treatment duration

- No impact of treatment rules was observed (in the virtual population) on the probability of having 1-6 relapses within 24 months treatment window

- Differences in the clinical relevant outcome appear small, suggesting that treatment postponements during Year 2 do not lead to loss of efficacy
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Postponing the Year 2 treatment is an appropriate risk mitigation measure for patients with lymphopenia Grade 2-4 at the end of Year 1

- **Alternative treatment rules** were investigated by obtaining projections for the Absolute Lymphocyte Counts (ALC) dynamics and Relapse Rate (RR) and in different scenarios.

- Results from this simulation analysis **support treatment guidelines** proposed to decrease risk of developing severe lymphopenia following cladribine treatment, while preserving cladribine efficacy on the considered clinical endpoint.

- As part of the **risk minimization strategy** to reduce the risk of lymphopenia, it is proposed to postpone cladribine treatment in year 2 until ALC have recovered to Grade 1 or better; should this not happen within 6 months, the treatment should be discontinued.
  - Very few subjects (1% or less) would not recover to Grade 1 or 0 within an additional 6 months.
  - In those who qualified for postponements (8% of virtual subjects), the proportion reaching Grade 3/4 lymphopenia at some time in the study is decreased (from 85% to 76%) when the mitigation rule is applied.
  - Such a delay of up to 6 months has essentially no effect on the probability of experiencing relapses during the second year of cladribine treatment.
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