Next Generation Health Technology Assessment

Project Title: Next Generation Health Technology Assessment to support patient-centred, societally oriented, real-time decision-making on access and reimbursement for health technologies throughout Europe

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TITLE: Report describing four available data sources in evidence synthesis for the evaluation of the effectiveness of treatments in relapsing-remitting multiple sclerosis

Subtitle: Data in relapsing-remitting multiple sclerosis

Introduction

A short description of the four available data sources

In CASE 3 we focus on optimal treatment for relapsing-remitting Multiple Sclerosis (MS): Previous synthesis of evidence from randomized controlled trials (RCTs) provided information about the effectiveness of 14 disease-modifying drugs (DMD) and yielded a treatment hierarchy (Tramacere et al. 2015). For four of the included drugs the manufacturing company (Biogen) provides individual patient data (IPD) from the RCTs as well as post-marketing real-world evidence from follow-up programs.

More specifically, we obtained data from

1. **Aggregated data** as published in randomised controlled trial included in the systematic review (Tramacere et al., 2015)
2. **Individual Patient Data (IPD) from six included randomized controlled trials** (Calabresi et al., 2014; Fox et al., 2012; Gold et al., 2012; Jacobs et al., 1996; Polman et al., 2006; Rudick et al., 2006). The data was provided by the sponsor (Biogen International GmbH) in a completely anonymized format.
3. We obtained **data from placebo-arms** from the Multiple Sclerosis Outcome Assessments Consortium (MSOAC) Placebo Database, a platform created and maintained by the critical path institute https://c-path.org/multiple-sclerosis-outcome-assessments-consortium-msoac-placebo-database-faq/. The platform contains placebo arm data from relapsing-remitting MS clinical trials, which includes data on basic demographics, performance outcome measures, clinician reported outcome measures, patient reported outcome measures, relapse information, and MS type. All data are fully anonymized. Once our application was approved, we obtained the data in the form of an excel spreadsheet. We are able to share the data with HTx members working on the same research with us, but not for research not covered in our application. However, the on-line process to obtain the data is so simple and quick that anybody from the consortium could get them. However, as the data is completely anonymized, we are not able to say where they come from (which trials). Biogen said that some of the RCTs for which we have IPD, their placebo arms are indeed included in the MSOAC, but we do not know which ones and we have no way to know. However, the model we are being developing using the MSOAC and the RCTs does not require independence between the two sources.

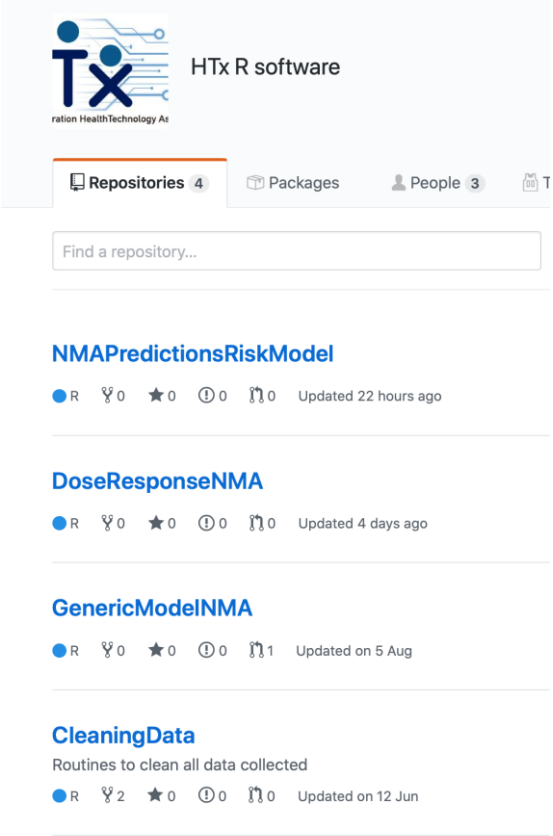
A fourth data source is described below. These data have not been yet obtained but we have received approval to our application to use them and we hope that very soon they will be available

4. We will use data from the **Swiss Multiple Sclerosis Cohort (SMSC)**. This is a long-term cohort (>10 years) representative of the MS population currently living in Switzerland.

They have put in place effective measures to limit drop-outs and it is focused on the continuous recruitment of MS patients. To enrol in the study patients must have a confirmed diagnosis of Multiple Sclerosis and be either without DMD or starting a DMD or already treated with Tysabri® or Gilenya®. The outcomes we are interested in and the patient characteristics are collected and reported in this study, making it a very suitable source of real-world evidence. The SMSC is governed by the Scientific Board with members representing 8 MS centres that provide data to SMSC. A description of SMSC can be found in (Disanto G et al. 2016).

Implementation

We obtained the data from the first three data sources. Data management was undertaken in the R software using self-programmed routines. We have created a GitHub repository "HTx R software" where various packages and function collections are stored.
https://github.com/htx-r
Within this directory there is a package `CleaningData` describing all data manipulation and coding processes employed in data source Nr 2 (the RCTs).
https://github.com/htx-r/CleaningData



Other packages are shown in the picture on the right and refer to the work done within WP2 which uses the relapsing-remitting MS data.

Hence, all data manipulation is tracked, and any changes and coding are documented. All our codes are open source. Working via GitHub packages and functions also ensures that any models and analyses done within WP2 in conjunction with WP1 are reproducible, subject to data availability. Note that data sources nr 3 and 4 are not in the public domain.

Results

Below is a description of the available datasets:

1. Aggregated data from published studies

Tramacere et.al 2015 conducted systematic review of the evidence about relapsing-remitting sclerosis (RRMS), which is followed by network meta-analysis (NMA) for 39 published RCTs. The majority of the included trials were short-term studies, with a median duration of 24 months. Twenty-four (60%) were placebo-controlled and 15 (40%) were head-to-head studies.

The NMA aimed to compare the efficacy of 15 DMDs used for patients diagnosed with RRMS. RCTs that are included evaluate one or more pharmacological interventions as monotherapy, compared to placebo or another active agent. All interventions that will be used in the analysis are depicted in Figure 1

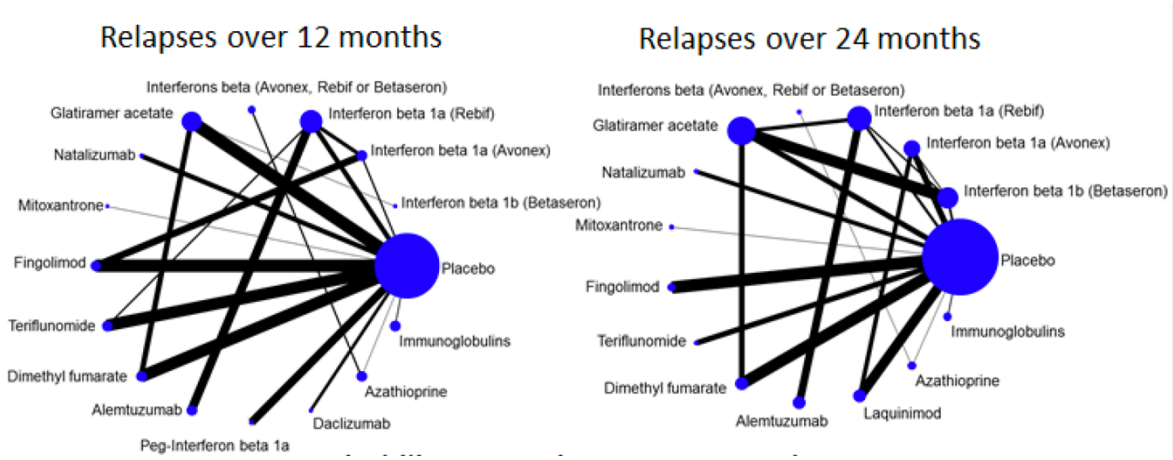


Figure 1: Network plots of treatment comparisons for relapse at one and two years

A total of 25,113 patients diagnosed with RRMS contributed to the analysis. Data collected from patients older than 18 years of age with a diagnosis of RRMS according to Poster 1983 or McDonald 2001 diagnosis criteria. Data included regardless of sex, degree of disability and duration of the disease. Data on several prognostic factors, such as time since diagnosis, EDSS, score, age, sex etc are also available. In addition to that, the relapses over 12 and 24 months after starting, switching treatment or after randomisation, are set as the primary outcomes of interest.

2. Individual Patient Data from randomised trials

We have six phase III randomized clinical trials, provided by BIOGEN: https://www.biogen.ch/, AFFIRM, CONFIRM, SENTINEL, ADVANCE, DEFINE and MSCRG. All of them include patients diagnosed with RRMS. All the relevant details of the studies have been published. Briefly, Table 1 presents the drugs compared in each study and the number of patients included in each study and in each treatment group. All six trials give information about relapses in one year. In addition, all of them, except for ADVANCE, give information about relapses in two years. The network plots for both relapse in one year and relapse in two years are shown in Figures 2 and 3.

Table 1. Drugs compared in each study with the number of patients in each study and in each treatment group. (n) is the sample size.

Study (n)	Drug 1 (n)	Drug 2 (n)	Drug 3 (n)
AFFIRM (939)	Natalizumab (627)	Placebo (312)	-
CONFIRM (1417)	Dimethyl fumarate (703)	Glatiramer acetate (351)	Placebo (363)
SENTINEL (1171)	Avonex (582)	Avonex & Natalizumab (589)	-
ADVANCE (1512)	Peginterferon Beta-1a (1013)	Placebo (499)	-
DEFINE (1234)	Dimethyl fumarate (n=826)	Placebo (408)	-
MSCRG (301)	Avonex (n=158)	Placebo (143)	-

3.

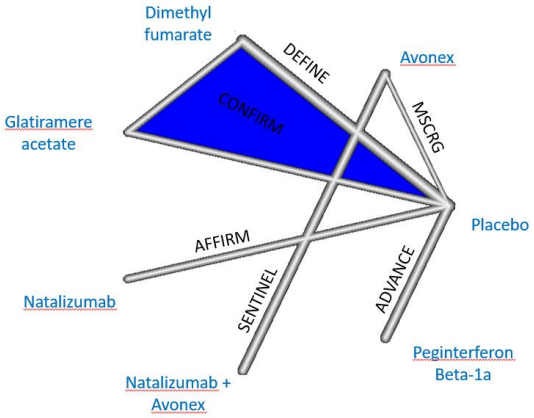


Figure 2. Network plot for confirmed relapsing MS in one year in patients diagnosed with relapsing-remitting MS.

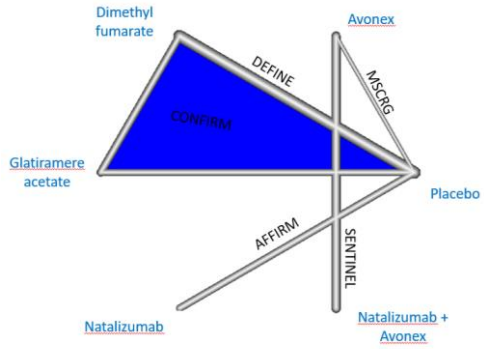


Figure 3. Network plot for confirmed relapsing MS in two years in patients diagnosed with relapsing-remitting MS.

Totally, there are 6574 patients available from these six RCTs. 4712 (71.6%) of them are females and 1862 (28.4%) are males. Table 2, shows some summary statistics of some important patients' characteristics included in the RCTs and Figure 4 shows the region's frequency in each one of the studies.

Table 2. Summary statistics for some basic patients' characteristics for the whole dataset (all 6 trials) (N=6574).

Patients' characteristics	Mean (sd)	Min-Max
Age (years)	37.4 (8.9)	18.0 – 61.0
Height (cm)	168.1 (9.5)	124.0 – 205.0
Weight (kg)	71.2 (16.9)	34.0 – 176.9

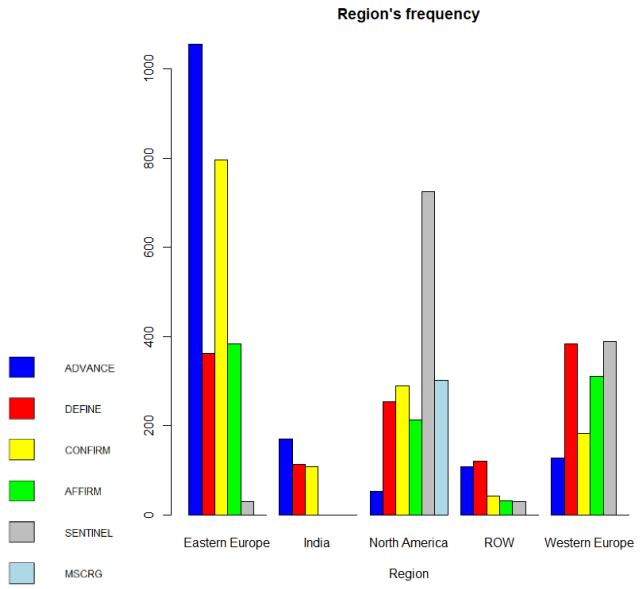


Figure 4. Region's frequency in each study.

There are also important prognostic factors relevant to the outcome (confirmed relapse MS) available, like baseline EDSS, Number of relapses 1 year prior to study, Years since onset of symptoms, Baseline Timed 25 Foot Walk Actual, Baseline 9 Hole Peg Test Average Score, Baseline PASAT 3 Actual. Figure 4 shows their distribution in the whole dataset.

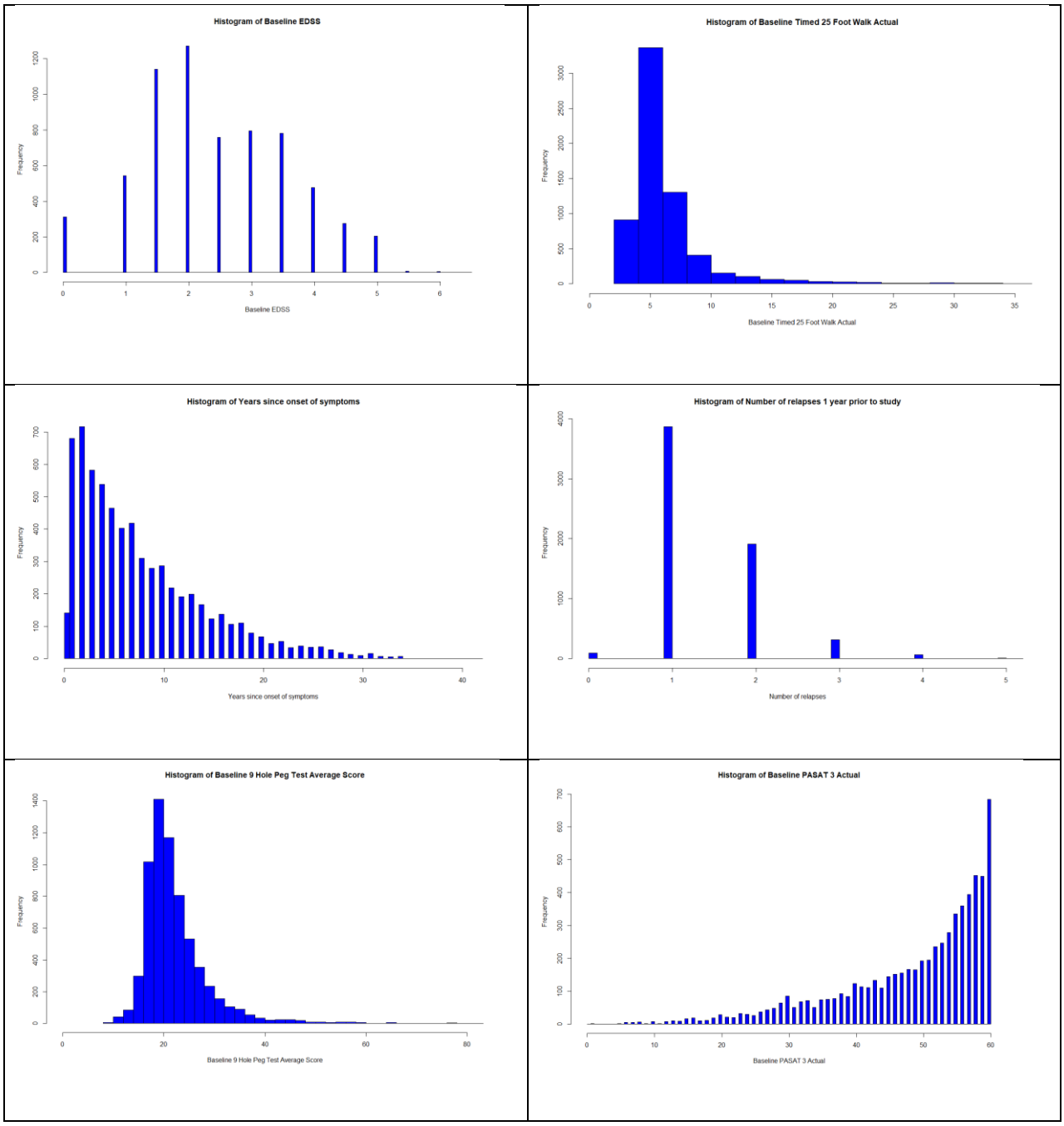


Figure 5. Distribution of 6 important prognostic factors relevant to the outcome in the whole dataset (N=6574).

3. Placebo arms from randomised trials

Critical Path Institute: https://c-path.org/ provided to us a placebo-arm dataset. This placebo-arm dataset includes in total 2465 patients from 9 clinical trials. It includes records from relapsing-remitting, secondary progressive, and primary progressive forms of MS. For our analyses we considered only patients diagnosed with relapsing-remitting MS. This dataset provides the time of each patient's relapses and information about the event (e.g. if it is suspected relapses, confirmed or unconfirmed relapses). 1083 patients give information about confirmed-RRMS in one year (Yes/No) and 1121 of them have information about confirmed-RRMS in two years (Yes/No). 1344 patients include no information about RRMS neither in one nor in two years. 1658 females and 807 males, from 18 to 72 years old (mean=41.77, standard deviation=10.41) are included in the dataset and age's distribution is shown in Figure 6. In addition, placebo-arm data include information about the race of patients (most of them white), as it is depicted in Figure 7.

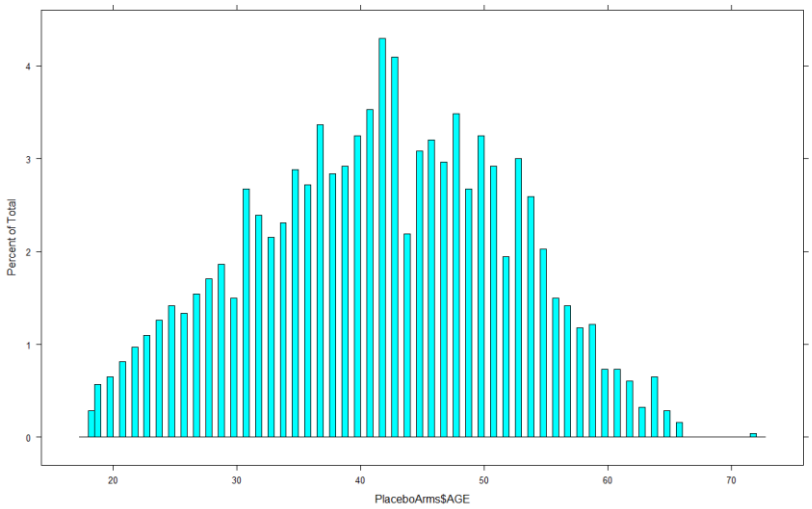


Figure 6. The distribution of age in the whole Placebo-arm dataset

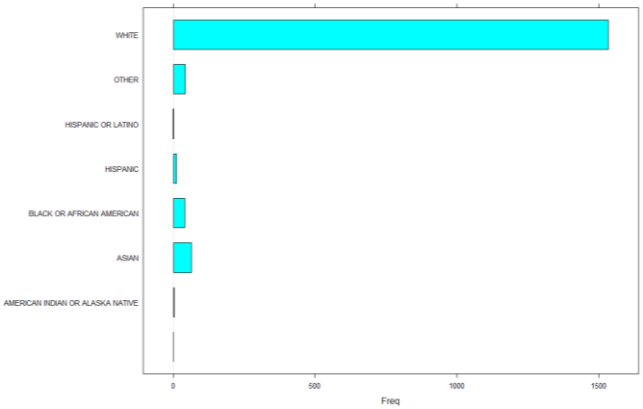


Figure 7. The frequency of the race of patients in Placebo-arm dataset

4. Real-world data from the Swiss MS cohort

The Swiss MS cohort-study (SMSC) is a prospective observational study conducted in seven centres across Switzerland (Disanto G et al. 2016). As we have not received the data yet, we are summarizing their description using information that the SMSC managing board shared with us and is available in (Disanto G et al. 2016).

From the individuals recruited to the study, we include patients diagnosed with RRMS according to McDonald criteria, 2010. Moreover, the participants may receive out of several disease modifying drugs (DMDs), which include natalizumab, fingolimod, dimethyl fumarate, teriflunomide and alemtuzumab. In addition to that, the first generation of injectable DMDs (interferon β-1b, interferon β-1a and glatiramer acetate) are also included in the study.
According to the above inclusion criteria, a total of 742 patients have been participated between June 2012 and July 2015. Only 32 patients (4.3%) have withdrawn from the study for several reasons. All patients had a median follow-up of 385 days. Twice as many women than men were included: that is 521 vs 221, respectively. The overall median age is 41 years. The characteristics of the sample are summarized in Table 3.

	Female (%)	Age median(IQR)	Days of follow-up median (IQR)	Disease Duration years median (IQR)	EDSS* median (IQR)
Total (n=742)	521 (70.2)	41.0 (32.7-48.9)	385 (0-734.8)	8.1 (3.2-14.0)	2.0 (1.5-3.0)

Table 3: Baseline characteristics of recruited individuals.

Fingolimod, natalizumab and injectable DMDs are the most common used DMDs for RRMS patients - for others the sample size is very small. For these DMDs, some descriptive data for incident of relapses is presented below in Table 2 for patients who started a DMD 2 years before baseline. The mean annualized relapse rate (number of relapses /treatment exposure time has been computed. In that, the mean ARR from Natalizumab was 0.09, for Fingolimod and for injectable DMDs 0.43.

Changes from the description of the data in the Grant Agreement

We have initially tried to receive Individual Patient Data (IPD) from Tysabri (Natalizumab) Observational Program. This plan has been changed (Biogen legal office declined our access request). As an alternative we have now applied to obtain data of similar nature (and even more suitable from the project) from the Swiss Multiple Sclerosis Cohort (SMSC). Our application was approved and we will receive the data as soon as we clear the ethics application process.

The Grant Agreement mentions another data source that is not available anymore ("synthetic data from patients included in the placebo arms of RCTS from Sylvia Lawry Centre"). We did and will not receive data from the Sylvia Lawry Centre, because they do not provide that data to anybody anymore. Instead, the data from MSOAC is obtain, and serves the same purpose.

Conclusions

To evaluate the relative effectiveness of the drugs for RRMS, we have available several datasets. These provide different information about the same research question and they seem to be compatible in terms of definitions of outcomes, patients and interventions. Their synthesis using methods from WP2 will shed light to the efficacy and effectiveness of the competing drugs.

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