

ANALYZING REAL WORLD DATA - CASE STUDY

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Agenda

- Drug & Disease Overview
- Look back with Clinical Trial Data
- Analysis Performed
- Understanding from the analysis
- Real World Data
- Analysis and Understanding
- What we see
- Future Work and Discussion

INTRODUCTION -

Sibasish Saha

Hobbies



SQL

??

Professional
Details



MS-Stat



Job



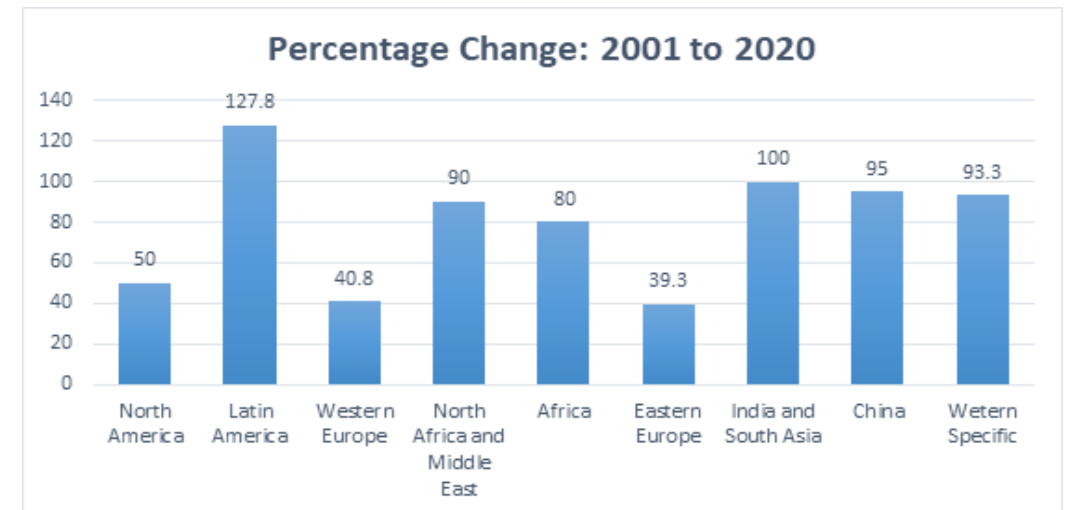
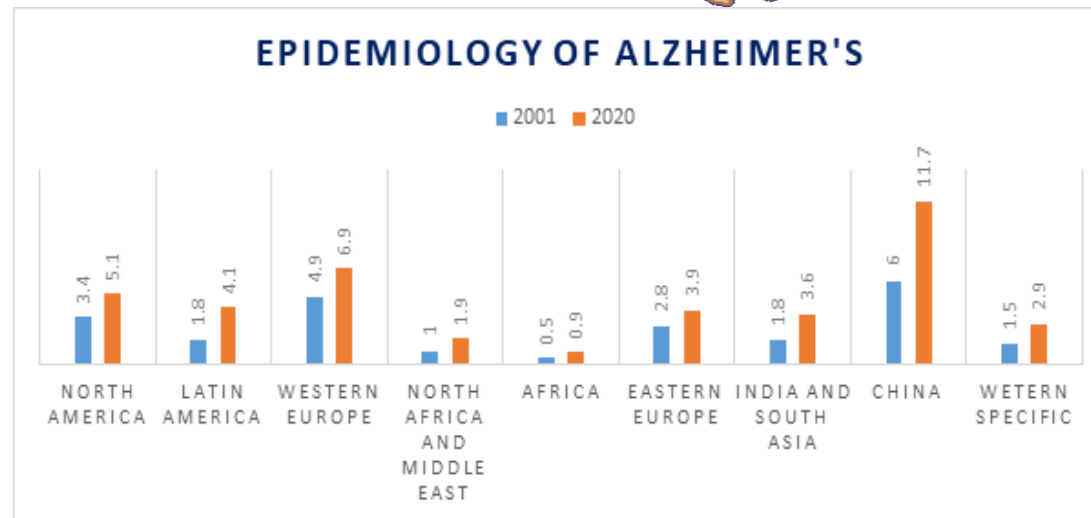
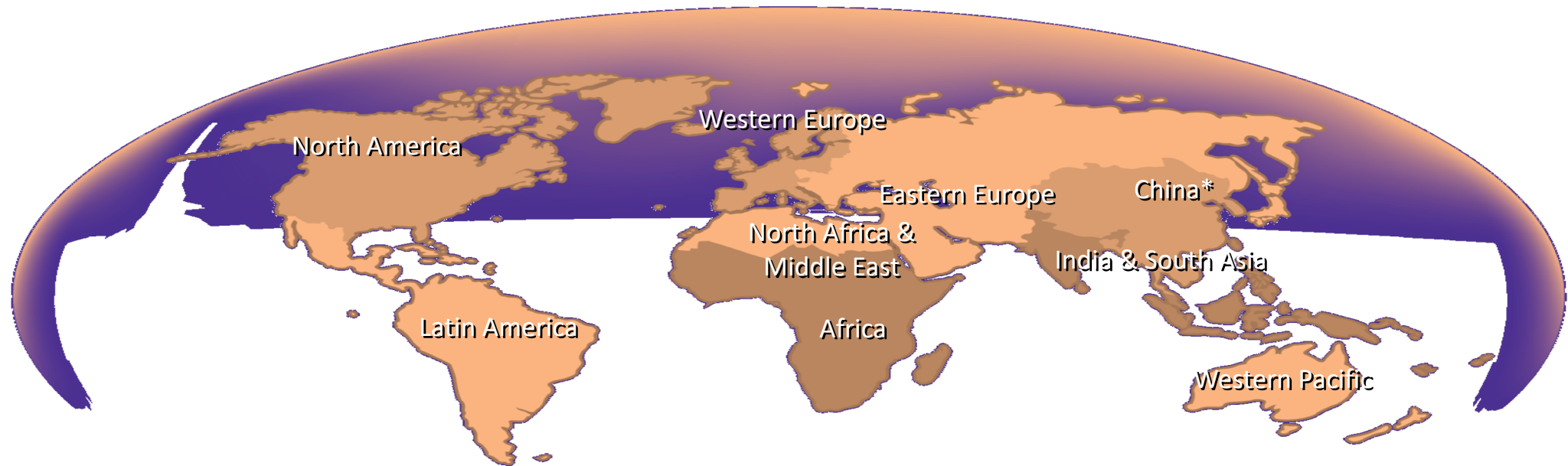
CensoredAs of now

2004 + 12

2005 + 12

2006 + 12

Drug & Disease Overview - Epidemiology



* & Developing Western Pacific Region. From Ferri et al, *Lancet* 2005;366:2112–2117.

Drug & Disease Overview - Alzheimer

Alzheimer's is a type of dementia that causes problems with memory, thinking and behavior.

Symptoms usually develop slowly and get worse over time, becoming severe enough to interfere with daily tasks.

Facts :

- Alzheimer's is the most common form of dementia.
- Alzheimer's is not a normal part of aging.
- Alzheimer's worsens over time.
- Alzheimer's has no current cure.
Treatments for symptoms are available and research continues.

Drug & Disease Overview - Exelon

- Exelon ([rivastigmine](#)) improves the function of nerve cells in the brain. It works by preventing the breakdown of a chemical that is important for the processes of memory, thinking, and reasoning. People with dementia usually have lower levels of this chemical.
 - Exelon is used to treat mild to moderate [dementia](#) caused by Alzheimer's (Alzheimer's disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks.) or [Parkinson's disease](#).
 - On 05-09-2007 Exelon Patch launched in the market in three dose format, 4.6 mg/24 hours, 9.5 mg/24 hours, 13.3 mg/24 hours.
-
- Memantine is a prescription drug used to treat moderate to severe confusion (dementia) related to Alzheimer's disease. It does not cure Alzheimer's disease, but it may improve memory, awareness, and the ability to perform daily functions.
 - This medication works by blocking the action of a certain natural substance in the brain (glutamate) that is believed to be linked to symptoms of Alzheimer's disease

Look back with Clinical Trial Data

[Study Details](#)[Tabular View](#)[Study Results](#)[Disclaimer](#)[? How to Read a Study Record](#)

Study Description

Go to 

Brief Summary:

The purpose of this study was to support the optimal use of rivastigmine patch in long-term treatment of Alzheimer's Disease in patients demonstrating functional and cognitive decline at the target maintenance dose of rivastigmine patch 10 cm².

Condition or disease 	Intervention/treatment 	Phase 
Alzheimer Disease	Drug: Rivastigmine 5 cm ² Drug: Rivastigmine 10 cm ² Drug: Rivastigmine 15 cm ² Drug: Placebo to 15 cm ² patch Drug: Placebo to 10 cm ² patch	Phase 3

Study Design

Go to 

Study Type : Interventional (Clinical Trial)

Actual Enrollment : 1584 participants

Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: Triple (Participant, Care Provider, Investigator)

Primary Purpose: Treatment

Official Title: A 48-Week, Multicenter, Randomized, Double-Blind, Parallel-Group Evaluation of the Comparative Efficacy, Safety, and Tolerability of Exelon® 10 and 15 cm² Patch in Patients With Mild to Moderate Alzheimer's Disease (AD) Showing Functional and Cognitive Decline

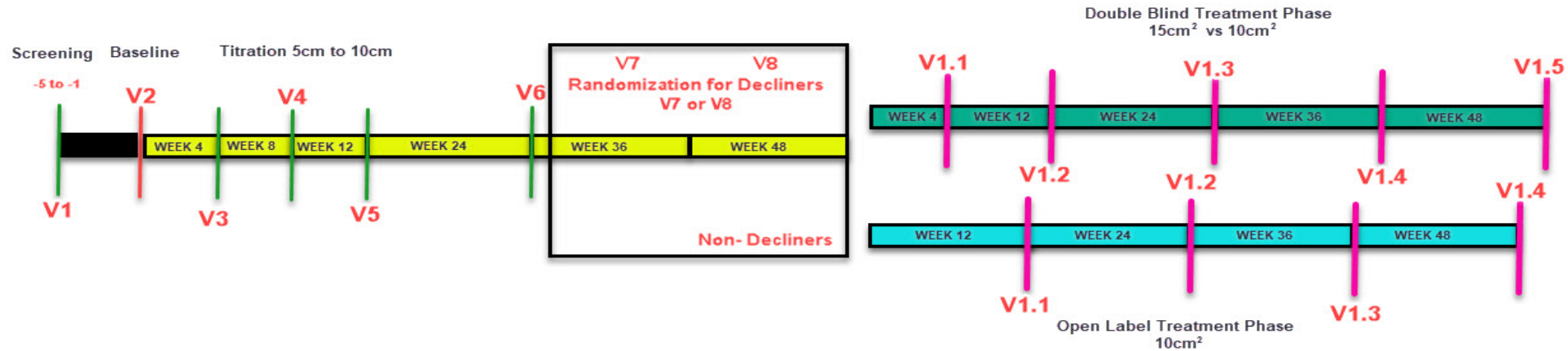
Study Start Date : June 2007

Actual Primary Completion Date : May 2011

Actual Study Completion Date : May 2011

Source : https://clinicaltrials.gov/ct2/show/study/NCT00506415?show_locs=Y

Look back Continues



Primary Outcome Measures ⓘ :

1. Change From Baseline in Alzheimer's Disease Assessment Scale-Cognitive (ADAS-Cog) Subscale at Week 48 of Double Blind Period
[Time Frame: Baseline and week 48 of double blind period]

The Alzheimer's Disease Assessment Scale-Cognitive (ADAS-cog) subscale comprises 11 items summed to a total score ranging from 0 to 70, with lower scores indicating less severe impairment. A negative change indicates an improvement from baseline.

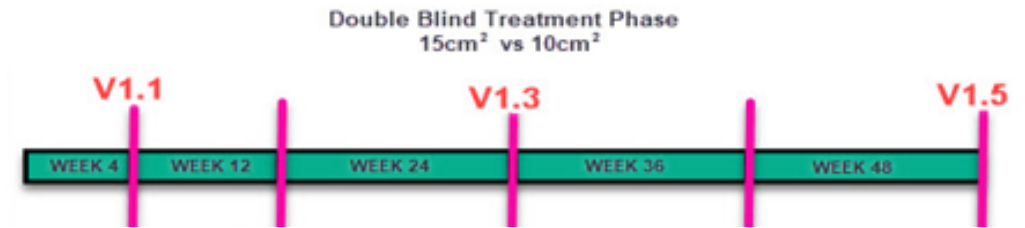
2. Change in Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL) Subscale Score From Baseline to Week 48 of Double Blind Period [Time Frame: Baseline and week 48 of double blind period]

The Alzheimer's Disease Cooperative Study-Instrumental Activities of Daily Living (ADCS-IADL) is a 16 item subscale of the caregiver-based ADCS-IADL scale, developed for the use in dementia studies. The ADCS-IADL total score ranges from 0 to 56, with higher scores indicating less severe impairment. A positive change indicates an improvement from baseline.

Look back Continues

Questions to answer

- What is the effect of Memantine?
- Is combination therapy better?
- Higher dose or Lower Dose with Memantine
- Does any one of those really slow down the progress.

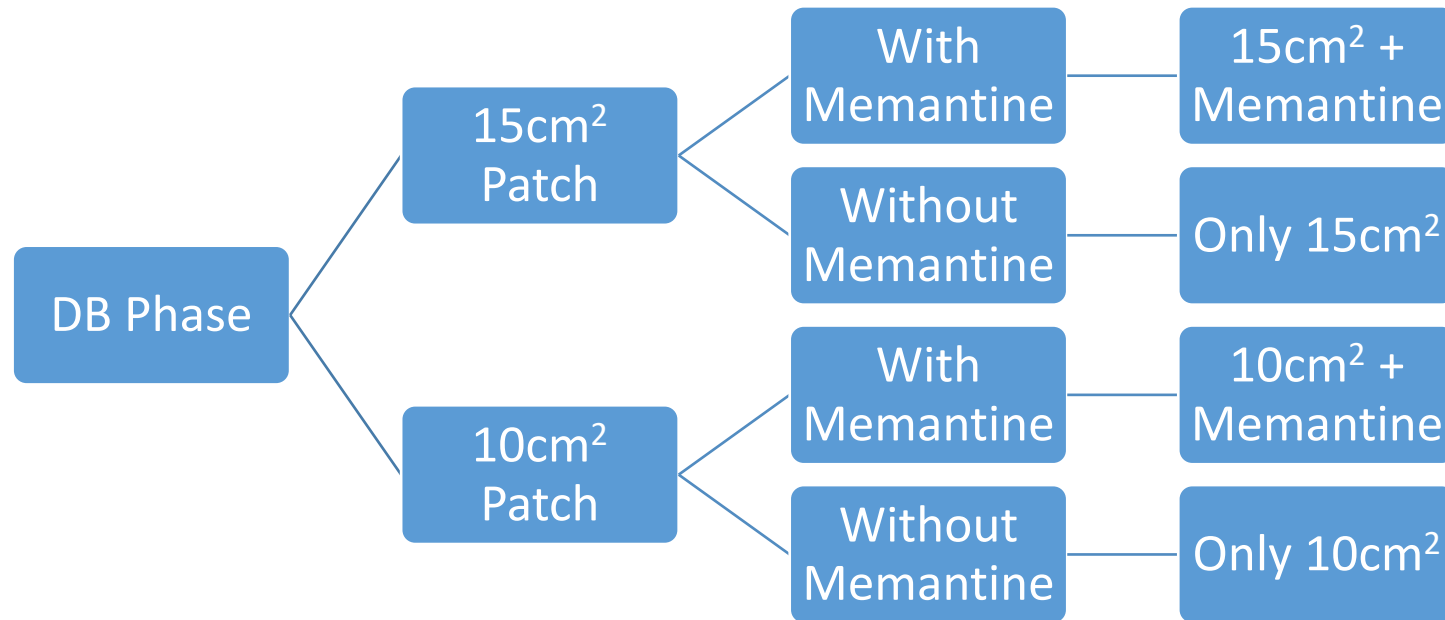


Challenge : Data is not fit to do the analysis as this is not balanced between treatment arms and also not collected for the purpose as well. Hence a balancing with respect to baseline characteristic is extremely important.

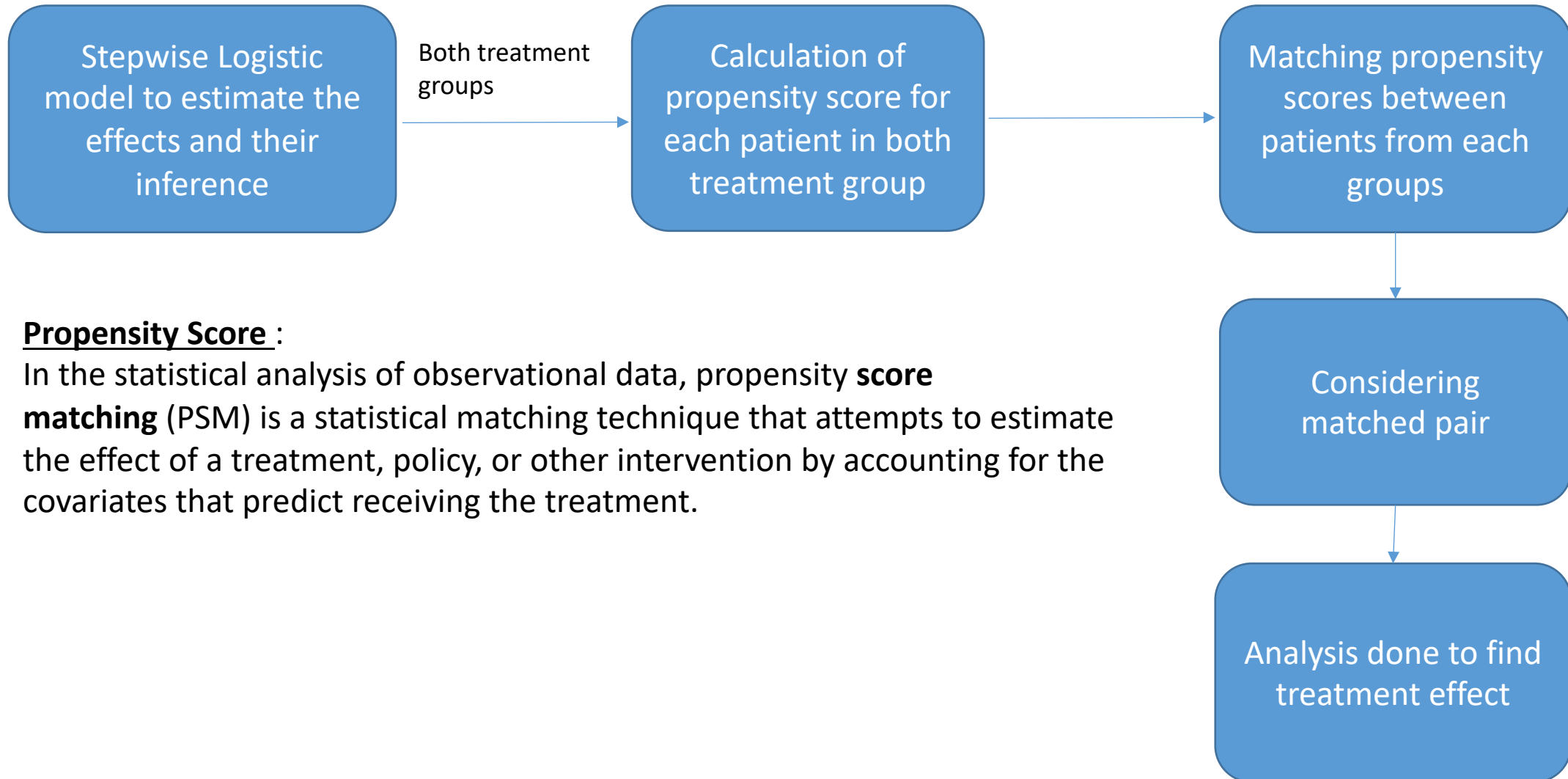
Analysis

Matched-Pair Analysis

An analysis which helps to group subjects in a study group and a comparison group with respect to key factors by individually pairing study subjects with the comparison group subjects.



Analysis - Continued



Propensity Score :

In the statistical analysis of observational data, propensity **score matching** (PSM) is a statistical matching technique that attempts to estimate the effect of a treatment, policy, or other intervention by accounting for the covariates that predict receiving the treatment.

Analysis - Continued

```
proc logistic data=comb outest = &outdt ;  
  class &class;  
  model &trt = &model / selection = stepwise slentry = 0.2 slstay = 0.1;  
  output out=logt1 p=phat lower=lcl upper=ucl predprob=(individual);  
run;
```

model : response variable and the explanatory effects, including covariates, main effects, interactions, and nested effects

selection : specifies the method used to select the variables in the model

slentry : significance level of the score chi-square for entering an effect into the model in the FORWARD or STEPWISE method

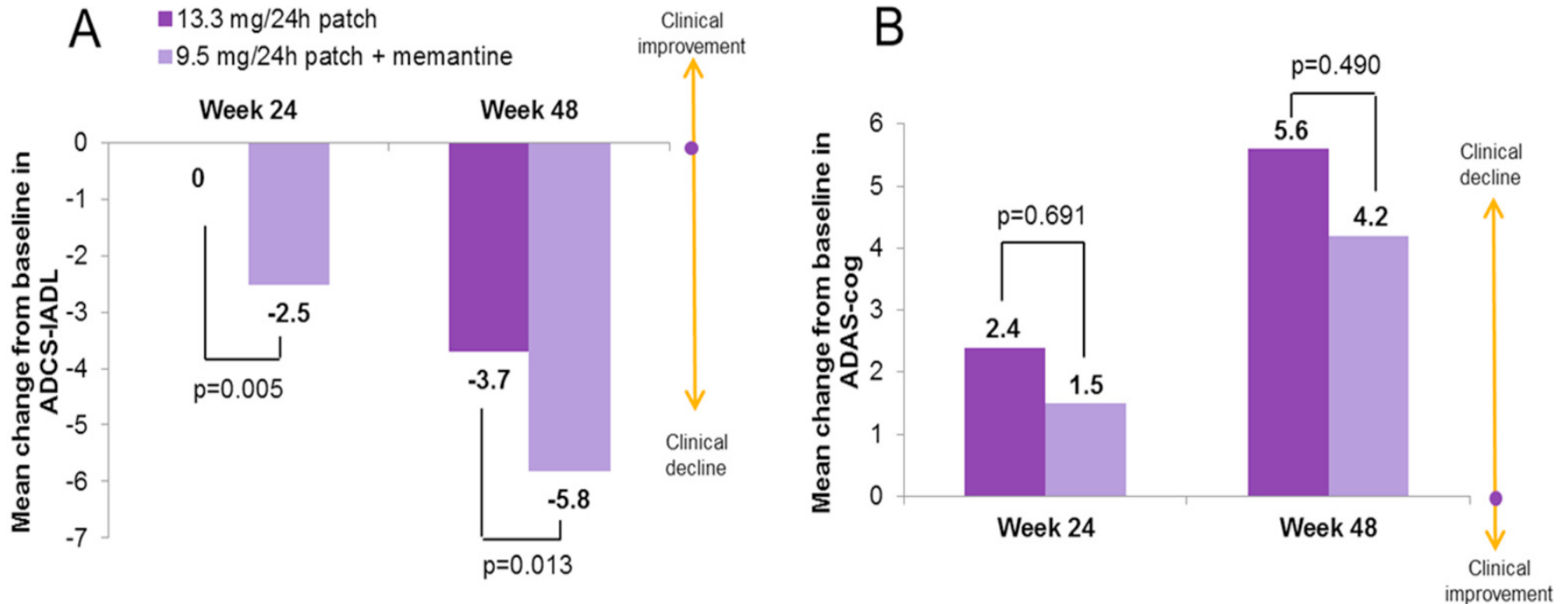
slstay : significance level of the Wald chi-square for an effect to stay in the model in a backward elimination step

predprob : predicted probabilities based on cumulative or individual

Comparing 15cm2 VS 10cm2+ Memantine

- **Methods:** In this retrospective analysis, patients declining and entering the double-blind phase, previously treated with 9.5 mg/24h patch during the initial open label phase, were matched 1:1 (memantine users versus non-memantine) by means of propensity scores. The change from baseline in ADCS-IADL scale and ADAS-cog subscale was assessed at Weeks 24 and 48 in patients treated with 13.3 mg/24h alone and those taking 9.5 mg/24h patch and [memantine](#) concomitantly (memantine was used at the investigator's discretion). The use of memantine was not randomized. Data analysis was performed using [ANCOVA](#) including factors for treatment, country and baseline score of the respective efficacy parameter. Safety evaluations included incidence of adverse events (AEs) and serious AEs (SAEs).
- **Results:** 142 patients were included (71 per group). Gender, race, age, BMI and MMSE were comparable between the two groups. 61.3% patients were female and 87.3% were ≥65 years. Patients treated with 13.3 mg/24h patch showed statistically greater benefit in function (ADCS-IADL) at weeks 24 and 48 versus those receiving concomitantly 9.5 mg/24h patch and [memantine](#) (Figure-1A). ADAS-cog outcomes were comparable between the two groups (Figure-1B). The incidence rate of AEs, AEs leading to discontinuation and SAEs were 63.4 vs 54.9%, 2.8 vs 4.2% and 8.5 vs 8.5% in 13.3 mg/24h patch alone versus 9.5 mg/24h patch with concomitant memantine, respectively.
- **Conclusions:** Based on patients matched by propensity scores, this analysis found greater IADL benefit in patients up-titrated from 9.5 mg/24h to 13.3 mg/24h patch as compared to those receiving 9.5 mg/24h patch and concomitant [memantine](#) throughout. **Although this analysis cannot replace a properly randomized trial, it suggests that a treatment regimen with up-titration from 9.5 mg/24h to 13.3 mg/24h patch may be more beneficial to AD patients compared to a regimen with combination of rivastigmine 9.5 mg/24h patch and memantine.**

Understanding



p-values are based on an analysis of covariance model adjusted for country and baseline score.

ADCS-IADL, Alzheimer's Disease Cooperative Study–Instrumental Activities of Daily Living; ADAS-cog; Alzheimer's Disease Assessment Scale–cognitive subscale

Comparing 10cm2 VS 10cm2+ Memantine

- A negative difference in DLSP(Difference in Least Square Mean) indicates greater improvement in Exelon 10cm2 as compared to Exelon 10cm2 + Memantine.
- During all visits the DLSP value was positive.
- At Week 48, Exelon 10 cm2 + Memantine working better.
- Overall impression, the combination therapy has better efficacy profile.....based on matched pair.

What we look forward

- We looked in clinical trial data with match pair analysis with limited number of patients.
- Post-launch of drug, there are huge volume of data in different Insurance, Claims, hospital, prescription database. We will look mainly towards analysis on patients' adverse event with a huge databank.
- For that the interest of research is the highest predefined Adverse events of Exelon and Exelon + Memantine
- As it is predefined, we will not consider any other possible confounding effects.

Real World Data



LifeLab
UK-based heart failure
database



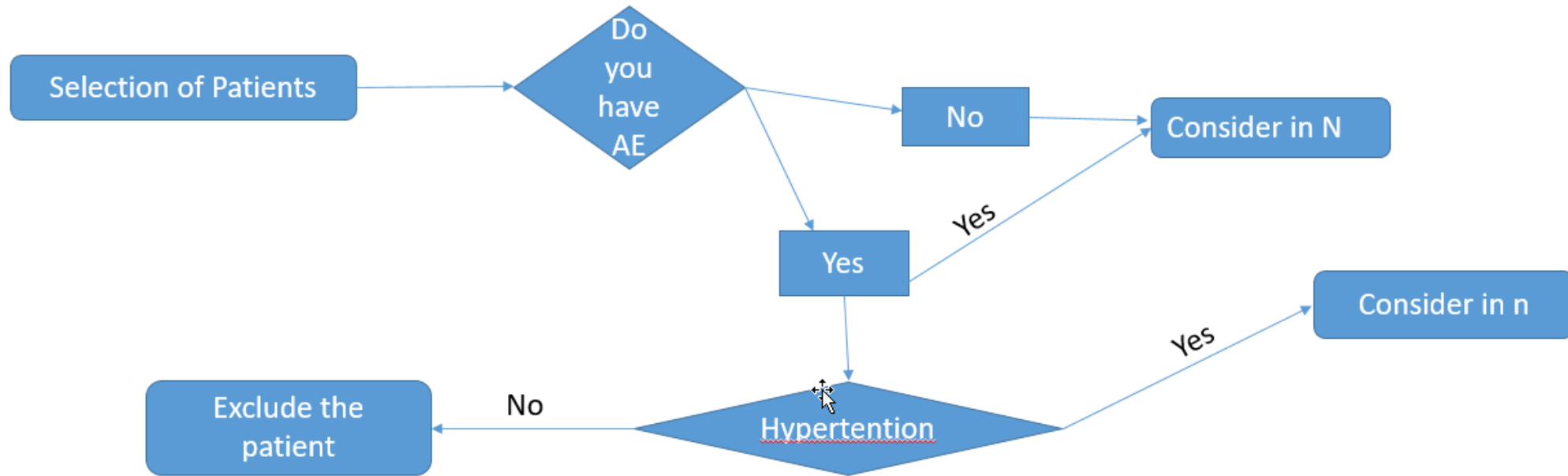
US Heart Failure
Caregiver Survey*



Where we start?

MarketScan	Optum
• Claim database	• Physician Note and Claim information
• Lack of demographic data and measurement values	• The measurement on efficacy parameters are there however, inconsistent format of data makes it difficult to run analysis.
• Post 2016, the data quantity is not great.	• Physician note captured directly from the prescription data. Good level of cleaning is mandatory before analysis.

Selection of patient



Selection of AE

- We have initially considered most frequent Adverse Event based on Exelon packaging insertions and some of the most frequent Adverse event from Real World Data for the use of the Exelon and Memantine.
- The most frequent Adverse events are Hypertension, Malaise and Fatigue, Hyperlipidemia, Urinary Tract Infection, Dementia, Chest Pain, Mental Disorder, Nausea and Vomiting etc.

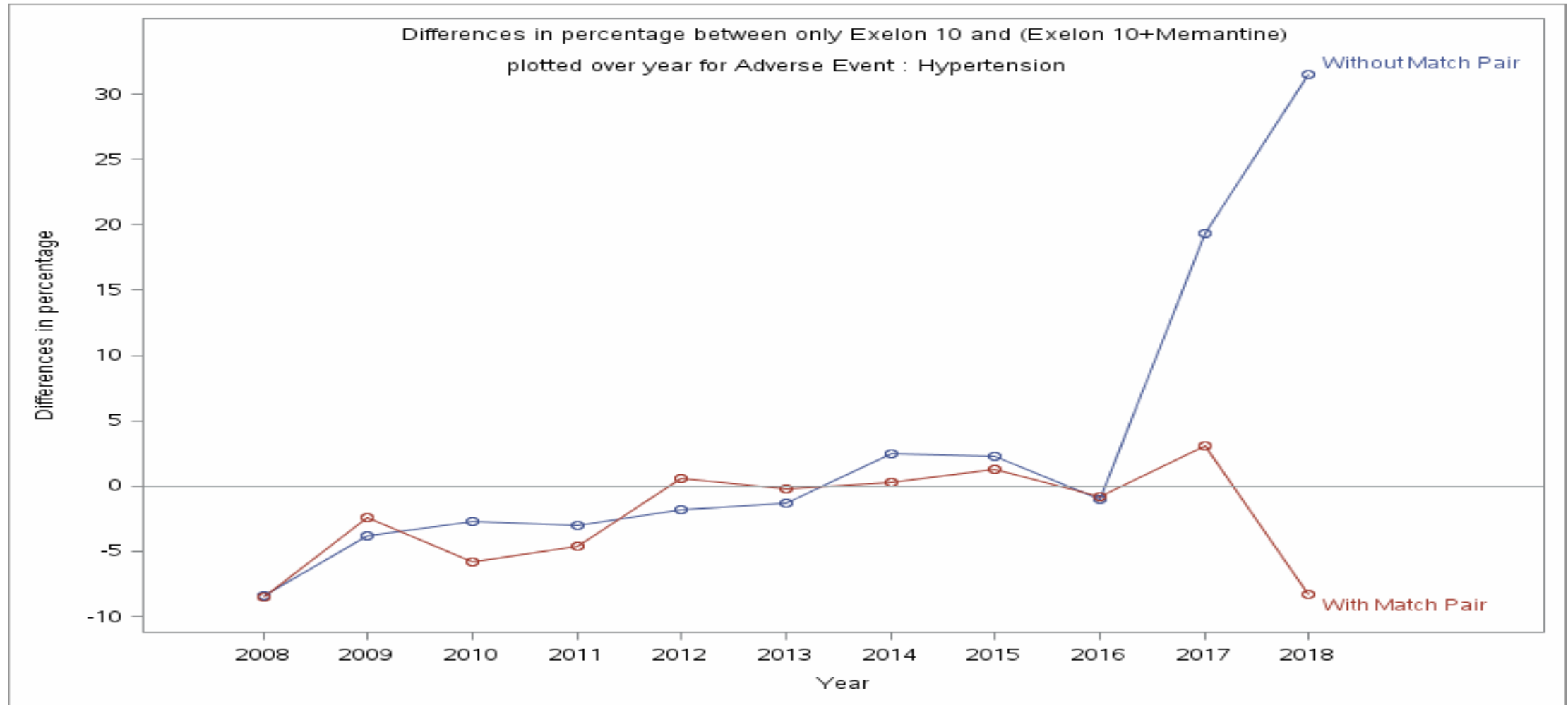
Heat map on #patient on different dose from Marketscan



Effect of Matched pair analysis

Before and after percentages

The SAS System



Future Work and Discussion

- Justification on adverse event frequency while Memantine used along with Exelon.
- Efficacy data from Prescription.....Use of Statistical methodology for mixed response using NLP.
- Treatment switching pattern including all generics launched 2015 onwards

Acknowledgement

We would sincerely thank Dr. Angshuman Sarkar(BioStatistics Site Head, GSK, India) for his advice and guidance behind this.

We Would also like to thank our team who has been backbone for this project. Some of the key inspiring personalities

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- Deepak Reddy(Group Lead, BioStatistics and Programming, Data Science, PLS, Novartis)
- Dr. Sanchayita Sadhu(Bio-Statistician) for her engagement on this project.

Thank You

-Listening to all suggestions and guidance..