PharmaSUG 2016 - Paper PO07

Creating Time to Event ADaM Dataset for a Complex Efficacy Endpoint in Multiple Sclerosis Therapeutic Area

Ittai Rambach, Teva Pharmaceuticals LTD., Netanya, Israel

ABSTRACT

This article presents my solution for the creation of Time to Event ADaM Dataset (ADTTE) for a complex efficacy endpoint – Time to Confirmed Disease Progression (CDP) which is evaluated by survival analysis, and is commonly used in Multiple Sclerosis (MS) therapeutic area studies.

CDP is defined as:

1. An increase from baseline of ≥1.0 points if the baseline EDSS was 5.0 points or less, or an increase of ≥0.5 point if the baseline EDSS was ≥5.5 points
2. The increase should be sustained for at least xx* months
3. Progression cannot be confirmed during a confirmed relapse

   * The exact definition should be defined in the study protocol and SAP (usually the sustained should be at least for 12 or 24 weeks).

In this article I first introduce the MS TA, explain the EDSS scale, and look in the Data – Neurological Assessments and Relapses. The main part of the article focuses on how to define the CDP by creating ADaM dataset for Neurological assessments (ADXS) and the Time to Event ADaM Dataset (ADTTE), with multiple censoring values and different event and censoring description. The traceability from ADTTE back to ADXS and to SDTM is discussed. This paper is intended for clinical programmers and statisticians while developing ADTTE for CDP, previous knowledge in ADaM standards is expected.

INTRODUCTION

In individuals with multiple sclerosis, physical and cognitive disability progressions are clinical and pathophysiological hallmarks of the disease. Despite shortcomings, particularly in capturing cognitive deficits, the Expanded Disability Status Scale is the assessment of disability progression most widely used in clinical trials.

MS PROGRESSION: EXPANDED DISABILITY STATUS SCALE (EDSS)

The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis. The scale has been developed by John F. Kurtzke. The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these.

Kurtzke defines functional systems as follows: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, other

THE EDSS SCALE

With the help of the FSS, the examiner rates patient's disability on the EDSS scale. It ranges from 0 to 10, with half points for greater specificity. Lower numbers indicate less severe disability. Higher numbers reflect a greater degree of disability, mostly in relation to mobility:

0 = Normal

1-1.5 = No disability, but some abnormal neurological signs

2-2.5 = Minimal disability

3-4.5 = Moderate disability, affecting daily activities, but you can still walk

5-8 = More severe disability, impairing your daily activities and requiring assistance with walking

8.5-9.5 = Very severe disability, restricting you to bed

10 = Death

It's important to recognize that a one-point change at the lower end of the scale reflects more subtle changes than at the upper end of the scale. For example, a one-point change between 2 and 3 is not as great a progression of disability as between 8 and 9. The EDSS score is not a linear scale.

SDTM DATASET FOR NEUROLOGICAL ASSESSMENT

The SDTM neurological raw data is combined from by-visit tests according to protocol e.g. FSS, Time 25 foot walk etc. (See Table 1), and occurrences category for relapses (See Table 2).

Table 1: Example of neurological SDTM dataset

USUBJID	XSSCAT	XSTEST	XSTESTCD	VISIT	XSDTC	XSORRES
MS_STUDY_10001	AMBULATION	AMBULATION SCORE	SCOREAMB	Baseline	2015-02-12	5.0
MS_STUDY_10001	BOWEL/ BLADDER FUNCTIONS	FUNCTIONAL SYSTEM SCORE	SCOREFSS	Baseline	2015-02-12	6.0
MS_STUDY_10001	BRAINSTEM FUNCTIONS	FUNCTIONAL SYSTEM SCORE	SCOREFSS	Baseline	2015-02-12	6.0
MS_STUDY_10001	CEREBELLAR FUNCTIONS	FUNCTIONAL SYSTEM SCORE	SCOREFSS	Baseline	2015-02-12	5.5
MS_STUDY_10001	PYRAMIDAL FUNCTIONS	FUNCTIONAL SYSTEM SCORE	SCOREFSS	Baseline	2015-02-12	6.0
MS_STUDY_10001	SENSORY FUNCTIONS	FUNCTIONAL SYSTEM SCORE	SCOREFSS	Baseline	2015-02-12	6.5
MS_STUDY_10001	VISUAL (OPTIC) FUNCTIONS	FUNCTIONAL SYSTEM SCORE	SCOREFSS	Baseline	2015-02-12	5.5
MS_STUDY_10001	EXPANDED DISABILITY STATUS SCALE	EDSS SCORE	SCOREDSS	Baseline	2015-02-12	5.5

Table 1. Neurological by-visit raw data

Table 2: SDTM dataset for relapse assessments

USUBJID	XSCAT	XSTEST	XSTESTCD	XSDTC	XSORRES
MS_STUDY_10001	RELAPSE	Onset date of suspected relapse	REL001	2015-05-14	2015-05-12
MS_STUDY_10001	RELAPSE	Neuroexam visit date for relapse	REL002	2015-05-14	2015-05-14
MS_STUDY_10001	RELAPSE	Did the subject exp a confirmed relapse	REL003	2015-05-14	Y
MS_STUDY_10001	RELAPSE	Approx. date of relapse stabilization	REL004	2015-05-14	2015-05-16
MS_STUDY_10001	RELAPSE	Neuroexam visit date for stabilization	REL005	2015-05-14	2015-05-17

Table 2. Occurrences relapse assessments

HOW TO DEFINE DISEASE PROGRESSION?

Confirmed Disease Progression (CDP), as measured by EDSS, is defined as:

1. An increase from baseline of ≥1.0 points if the baseline EDSS was 5.0 or less, or an increase of ≥0.5 point if the baseline EDSS was ≥5.5 points
2. The increase should be sustained for at least xx* weeks
3. Progression cannot be confirmed during a confirmed relapse

   * The exact definition should be defined in the study protocol and SAP (usually the sustained should be at least for 12 or 24 weeks).

EXPLANATION OF CDP

For the explanation below we consider:

- 12 weeks progression as a confirmed disease progression
- The duration of the study is 16 weeks.

Figure 1: Progression sustained for 12 weeks, with no relapse during confirmation date

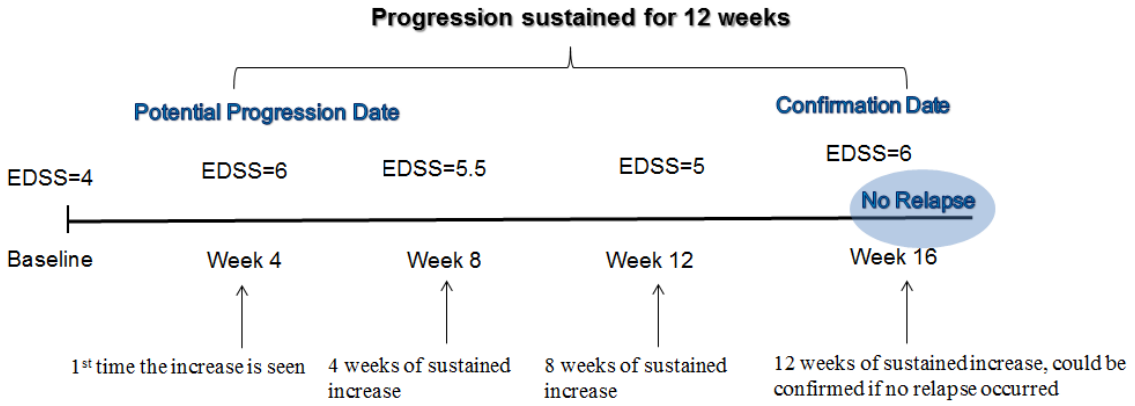

Figure 1. Confirmed disease progression

In figure 1, the patient enters the study with baseline EDSS score of 4, after 4 weeks he has an increase of 2 points from baseline to EDSS score of 6. This point is a potential disease progression. To make it a confirmed disease progression, the progression should be sustained for at least 12 weeks. The next visit is after 4 weeks and the score is 5.5 which mean an increase from baseline of more than 1 is still sustained. The EDSS score for week 12 (8 weeks from the potential progression) is 5, still sustained. The EDSS score for Week 16 (12 weeks from potential progression) is 6.

We have 12 weeks of sustained progression, but we still need to check that the EDSS assessment used for confirmation of this progression didn't occur during a confirmed relapse. This could be easily done by evaluating whether the EDSS assessment date falls between the onset and stop date of a relapse.

In figure 1, the EDSS measurement taken for confirmation, was not taken during relapse, therefore we can confirm the disease progression. However, if the EDSS assessment at week 16 would have been taken during a relapse, then we would need to continue scan the next EDSS measurements, until we have an assessment that could be used for confirmation of the disease progression (taken into account that all the records till that point show the required increase from baseline in EDSS). In this case, we still have the same potential progression date (week 4).

Defining the date of progression

Since our analysis endpoint is the time to confirmed disease progression we need to define the date of progression.

Please note that the date of progression for time to CDP, is the date where potential progression first appears (week 4 in figure 1), and not the confirmation date (week 16 in figure 1).

DIFFERENT CENSORING EXAMPLES

1. In figure 2, we have 12 weeks of sustained progression, without confirmation, due to relapse.

   The censoring description is unconfirmed progression.

Figure 2: Progression sustained for 12 weeks, but can't be confirm due to relapse during confirmation date

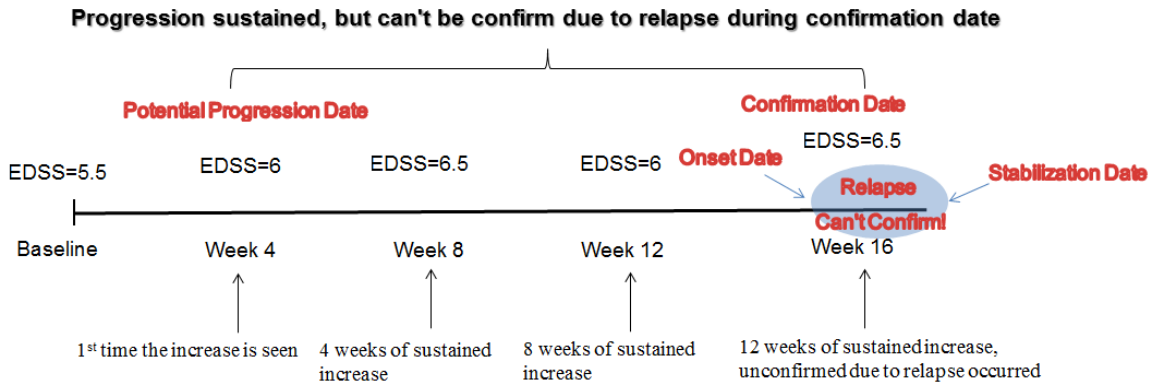

Figure 2: Unconfirmed disease progression

2. If progression didn't occur in one of the measurements (e.g. no change from baseline), we stop the scan, for that sequence, and potential progression declares the next time we see a progression.

   In figure 3, we have a case where a sequence was broken (week 8), a new potential progression date was found (week 12), and it was censored at week 16.

Figure 3: Progression didn't sustain, new potential progression date in week 12

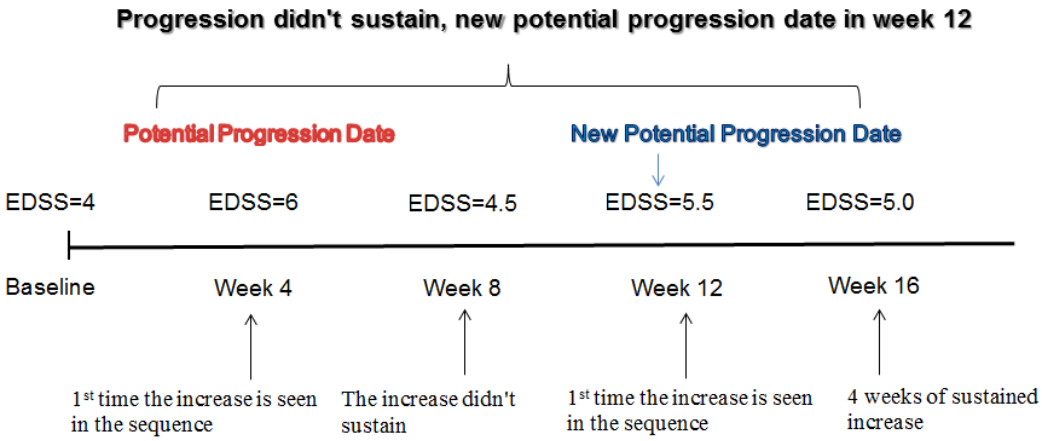

Figure 3. Progression didn't sustain

Defining the date of censoring for unconfirmed disease progression

The analysis date (ADT) is the date of potential progression and not the date of censoring.
In figure 3, the analysis date is the date of the new potential progression (week 12).

3. If there's no progression at the time of censoring, we use the last EDSS assessment prior to censoring.

   In figure 4 it's the assessment of week 16.

Figure 4: No Progression (Censored at week 16)

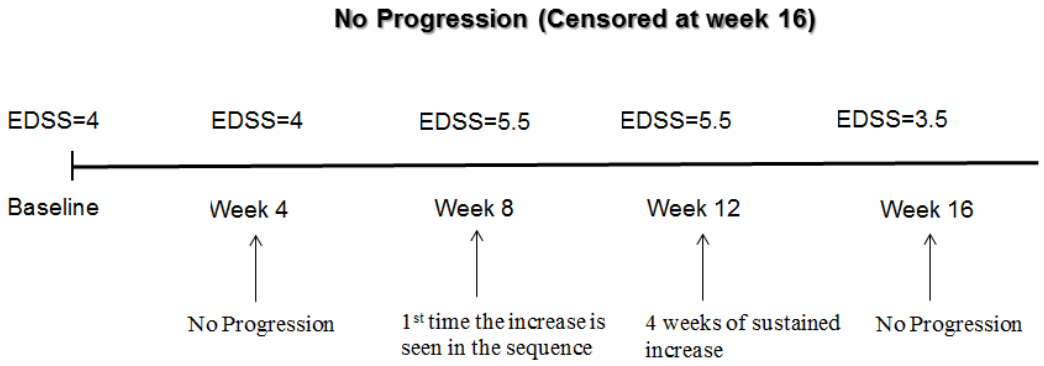

Figure 4. No progression

4. If there's no post baseline EDSS value, the randomization date is taken

CREATING NEUROLOGICAL ANALYSIS DATASETS

Before the creation of ADTTE for CDP we need to create an ADaM dataset for the neurological assessments and relapses (ADXS).

After we find the baseline assessment, we create a Criterion flag (CRIT1/2/FL) to indicate if the EDSS assessment has CRIT1="Increase in EDSS of ≥1.0 points from baseline if EDSS at entry is ≤ 5.0", or CRIT2="Increase in EDSS of ≥0.5 points from baseline if EDSS at entry is ≥ 5.5".

We also need to have a second Criterion Flag (CRIT3/FL) to indicate if the assessment was during confirmed relapse. We need to find the time frame of onset and stabilization of the relapse and if the assessment was performed during this period we populate the criterion with CRIT3="Assessment performed during confirmed relapse".

Table 3: Neurological analysis dataset (ADXS), the based for ADTTE

USUBJID	PARAM	PARAMCD	AVISIT	ADT	AVAL	ABLFL	CRIT1	CRIT2	CRIT3	ASEQ
MS_STUDY_10001	EDSS SCORE	SCOREDSS	Baseline	12FEB2015	4.0	Y				43
MS_STUDY_10001	EDSS SCORE	SCOREDSS	Week 4	14MAR2015	6.0		Increase in EDSS of >=1 point from baseline if EDSS at entry is <=5.0			44
MS_STUDY_10001	EDSS SCORE	SCOREDSS	Week 8	21APR2015	5.5		Increase in EDSS of >=1 point from baseline if EDSS at entry is <=5.0			45
MS_STUDY_10001	EDSS SCORE	SCOREDSS	Week 12	14MAY2015	5.0		Increase in EDSS of >=1 point from baseline if EDSS at entry is <=5.0			46
MS_STUDY_10001	EDSS SCORE	SCOREDSS	Week 16	15JUN2015	6.0		Increase in EDSS of >=1 point from baseline if EDSS at entry is <=5.0			47
MS_STUDY_10002	EDSS SCORE	SCOREDSS	Baseline	20JUN2015	5.5	Y				29
MS_STUDY_10002	EDSS SCORE	SCOREDSS	Week 4	22JUL2015	6.0			Increase in EDSS of >=0.5 point from baseline if EDSS at entry is >=5.5		30
MS_STUDY_10002	EDSS SCORE	SCOREDSS	Week 8	21AUG2015	6.5			Increase in EDSS of >=0.5 point from baseline if EDSS at entry is >=5.5		31
MS_STUDY_10002	EDSS SCORE	SCOREDSS	Week 12	22SEP2015	6.0			Increase in EDSS of >=0.5 point from baseline if EDSS at entry is >=5.5		32
MS_STUDY_10002	EDSS SCORE	SCOREDSS	Week 16	21OCT2015	6.5			Increase in EDSS of >=0.5 point from baseline if EDSS at entry is >=5.5	Assessment performed during confirmed relapse	33

MS_STUDY_10003	EDSS SCORE	SCOREDSS	Baseline	14OCT2015	4.0	Y				13
MS_STUDY_10003	EDSS SCORE	SCOREDSS	Week 4	12NOV2015	4.0					14
MS_STUDY_10003	EDSS SCORE	SCOREDSS	Week 8	13DEC2015	5.5		Increase in EDSS of >=1 point from baseline if EDSS at entry is <=5.0			15
MS_STUDY_10003	EDSS SCORE	SCOREDSS	Week 12	15JAN2016	5.5		Increase in EDSS of >=1 point from baseline if EDSS at entry is <=5.0			16
MS_STUDY_10003	EDSS SCORE	SCOREDSS	Week 16	13FEB2016	3.5					17
MS_STUDY_10004	EDSS SCORE	SCOREDSS	Baseline	24SEP2015	5.5	Y				5

Table 3. Neurological analysis dataset (ADXS) – EDSS category

In table 4, ADT for the relapse category is the date of neurological assessment, while AVALC is the actual date for onset and stabilization of the relpase.

Table 4: Relapse category in analysis dataset (ADXS)

USUBJID	PARAM	PARAMCD	AVISIT	ADT	AVALC
MS_STUDY_10001	Onset date of suspected relapse	CREL001		08AUG2015	05AUG2015
MS_STUDY_10001	Neuroexam visit date for relapse	CREL002		08AUG2015	08AUG2015
MS_STUDY_10001	Did the subject exp a confirmed relapse	CREL003		08AUG2015	Y
MS_STUDY_10001	Approx. date of relapse stabilization	CREL004		08AUG2015	10AUG2015
MS_STUDY_10001	Neuroexam visit date for stabilization	CREL005		08AUG2015	11AUG2015
MS_STUDY_10002	Onset date of suspected relapse	CREL001		18OCT2015	15OCT2015
MS_STUDY_10002	Neuroexam visit date for relapse	CREL002		18OCT2015	18OCO2015
MS_STUDY_10002	Did the subject exp a confirmed relapse	CREL003		18OCT2015	Y
MS_STUDY_10002	Approx. date of relapse stabilization	CREL004		18OCT2015	25OCT2015
MS_STUDY_10002	Neuroexam visit date for stabilization	CREL005		18OCT2015	25OCT2015

Table 4. ADXS – analysis relapse assessments

CREATING ADTTE FOR CDP

For the creation of ADTTE we use ADSL and ADXS.

These are the 4 cases of event or censoring:

Event

- CNSR=0 (Confirmed Disease progression)

  ADT - The date of progression assessment date that lead to confirmation

Censor

- CNSR=1 (Unconfirmed Disease progression)

  ADT - The date of first potential progression assessment date

- CNSR=2 (No progression)

  ADT – Last EDSS assessment date

- CNSR=3 (No post baseline EDSS assessment)

  ADT – Randomization Date

AVAL is calculated as the difference between ADT and randomization date (STARTDT).

See an example in table 5.

Table 5: Example of ADTTE based on ADXS and ADSL

USUBJID	PARAM	PARAMCD	AVAL	ADT	STARTDT	CNSR	EVNTDESC	CNSDTDSC	TRTP	SRCDOM	SRCVAR	SRCSEQ
MS_STUDY_10001	Time to 12-weeks CDP as Measured by EDSS (days)	TTCDPEDS	92	14MAR2015	12FEB2015	0	Confirmed disease progression		P	ADXS	ADT	44
MS_STUDY_10002	Time to 12-weeks CDP as Measured by EDSS (days)	TTCDPEDS	86	22JUL2015	20JUN2015	1	Unconfirmed disease progression	Onset date of unconfirmed progression	B	ADXS	ADT	30
MS_STUDY_10003	Time to 12-weeks CDP as Measured by EDSS (days)	TTCDPEDS	48	13FEB2016	14OCT2015	2	No progression	Last EDSS evaluation date	A	ADXS	ADT	25
MS_STUDY_10004	Time to 12-weeks CDP as Measured by EDSS (days)	TTCDPEDS	1	24SEP2015	24SEP2015	3	No post-baseline assessment	Randomization date	A	ADSL	RANDDT	

Table 5. ADTTE analysis dataset

MULTIPLE VALUES FOR CENSORING AND DIFFERENT EVENT AND CENSORING DESCRIPTION

We used multiple values for Event description (EVNTDESC) and Censoring Description (CNSDTDSC).

First, let's discuss why we use both event and censoring descriptions?

According to the CDISC ADaM guideline:

Event or censoring description should describe the event of interest or an event that warrants censoring.

The censor date description should be populated if the censoring date is different from the event that warrants censoring.

In other words: The analysis censoring date (ADT) is different from the date of the event causing the censoring.

For example, unconfirmed disease progression due to study completion described in EVNTDESC variable, and the analysis censoring date (ADT) is the onset of unconfirmed progression, and it's described in CNSDTDSC variable.

The analysis censoring date (ADT) in our case is different for 3 cases:

- Unconfirmed disease progression – In this case the analysis date is the onset date of the unconfirmed progression
- No progression – In this case the analysis date is the Last EDSS evaluation date
- No post-baseline assessment - In this case the analysis date is the Randomization date

Having both variables (EVNTDESC and CNSDTDSC) is much more reviewer friendly for programmer, statistician and regulatory review.

SOURCE VARIABLES – IMPROVE TRACEABILITY

To improve the traceability of the data from ADTTE to SDTM we use ADaM source variables: SRCDOM, SRCVAR, and SRCSEQ.

1. For both CDP and unconfirmed CDP the analysis date is the first progression in the sequence
   - SRCDOM="ADXS"
   - SRCVAR="ADT"
   - SRCSEQ – ASEQ of the first EDSS measurement with progression, in the sequence
2. For Censoring while no progression occurred
   - SRCDOM="ADXS"
   - SRCVAR="ADT"
   - SRCSEQ – ASEQ of the last EDSS measurement from ADXS
3. For Censoring while no post baseline assessment
   - SRCDOM="ADSL"
   - SRCVAR="RANDDT"
   - SRCSEQ – Missing, because the source is ADSL

CONCLUSION

Time to CDP is in common use as survival analysis endpoint in multiple sclerosis disease studies. I've presented solution for the creation of ADTTE based on my experience. It may have different approaches and solutions.

This approach complies with ADaM standard for Time to Event dataset, gives the statisticians an easy platform to perform analysis including sensitivity analysis by using multiple values for censoring and makes it clear for the reviewers to understand the traceability of the data that has been used for analysis.

REFERENCES

- CDISC Analysis Data Model, Version 2.1, available at http://www.cdisc.org
- The ADaM Basic Data Structure for Time-To-Event Analysis, available at http://www.cdisc.org
- Brucken Nancy, Slagle Paul. 2012. “Creating the Time to Event ADaM Dataset: The Nuts and Bolts”. PharmaSUG 2012. available at http://www.pharmasug.org/proceedings/2012/HW/PharmaSUG-2012-HW03.pdf
- https://en.wikipedia.org/wiki/Expanded_Disability_Status_Scale
- http://www.webmd.com/multiple-sclerosis/guide/disability-measured

ACKNOWLEDGMENTS

I would like to thank Yulia Sidi, from Teva Biostatistics group for her contribution in developing this method.

RECOMMENDED READING

The ADaM Basic Data Structure for Time-To-Event Analysis, available at http://www.cdisc.org

CONTACT INFORMATION

Your comments and questions are valued and encouraged. Contact the author at:

Name: Ittai Rambach
Enterprise: Teva Pharmaceuticals LTD.
Address: 12 Hatrufa St.
City, State ZIP: Netanya, Israel
Work Phone: 972(0)98921787
E-mail: ittai.rambach@tevapharm.com