Expectation of a Rare Event

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The Story Begins …

- TYSABRI® was approved in US for treatment of multiple sclerosis in November 2004
- Approval received after completion of one year interim analyses on a secondary endpoint for 2 two-year trials
  - Accelerated and contingent on results of the primary endpoint at 2 years in both trials.
- Based on:
  - Outstanding efficacy
    - 66% reduction in relapse rate in monotherapy trial
    - 54% reduction in relapse rate in add-on trial
  - Relatively clean safety profile
    - Low incidence of hypersensitivity reactions
    - Some increase in serious infections

Reports of PML

- In February 2005, within 3 months of approval, Biogen Idec received 2 reports of Progressive Multifocal Leukoencephalopathy (PML) in subjects participating in the clinical trials
  - PML is a rare viral infection caused by the reactivation of a common virus (JCV) within the central nervous system
  - It occurs in patients with severely compromised immune systems (AIDS, transplant, some drugs)
  - PML causes the loss of white matter (myelin) in multiple areas of the brain
  - Symptoms are clumsiness; progressive weakness; and visual, speech, and sometimes, personality changes
  - Typically leads to life-threatening disability and death over weeks to months
  - A positive diagnosis of PML can be made on brain biopsy, or by combining observation of a progressive course of the disease, consistent white matter lesions visible on a magnetic resonance image (MRI) scan, and the detection of the JC virus in spinal fluid.

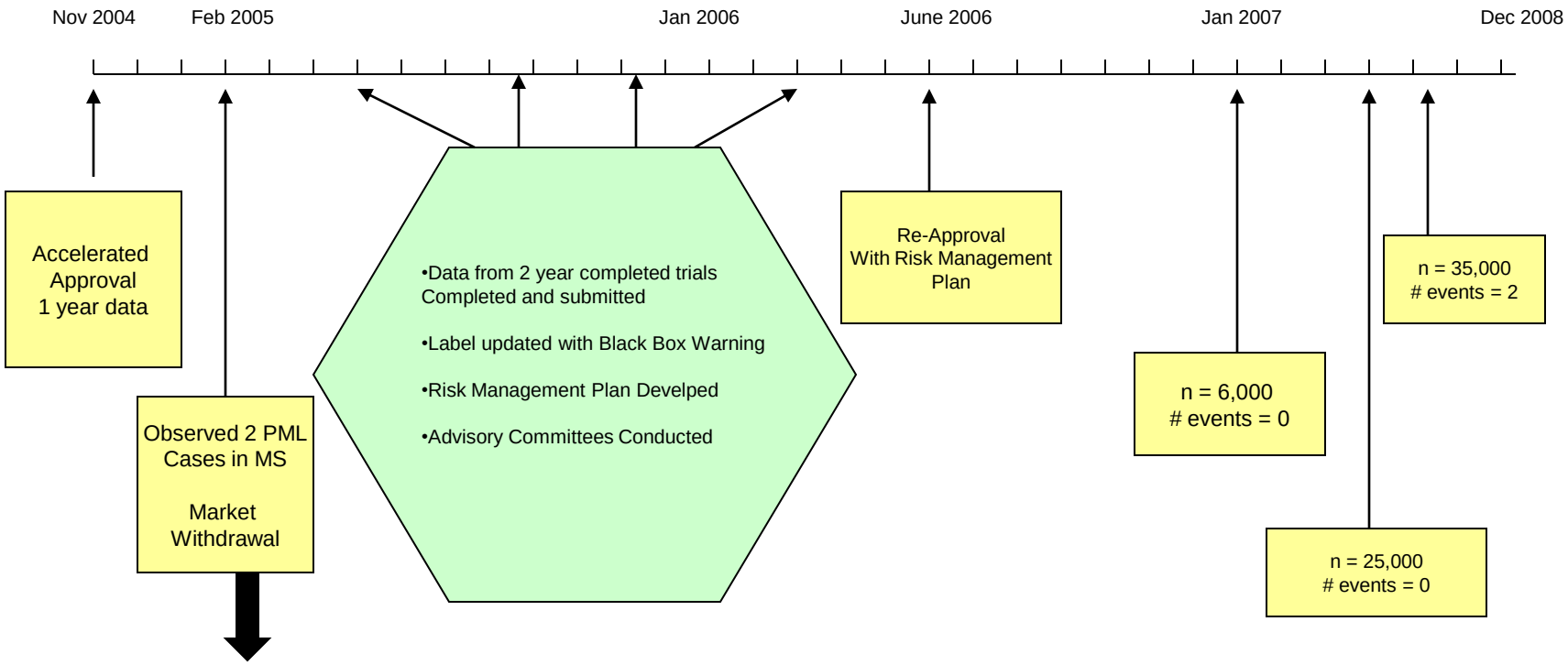
Next Steps

- PML was a new and unexpected very serious adverse event
- Biogen Idec made the decision to take TYSABRI® off the market
- Detailed investigation of all SAEs reported in trials to date was carried out
  - One further case identified in a subject in a Crohn's disease study
- Dosing suspended in all clinical trials
  - All subjects who had received TYSABRI® in Phase III trials were invited back for a safety assessment with a brain MRI
  - Systematic review of safety in approximately 3000 patients and analysis of MRIs identified no further PML cases

(Re-) Approval

- Efficacy and safety data from the second year of the Phase III trials were submitted
- Effect on relapse rate was maintained in the second year
  - 67% reduction in monotherapy trial
  - 56% reduction in add-on trial
- Addition of data showing a reduction in the risk of disease progression (2 year endpoint)
  - 42% reduction in monotherapy trial
  - 24% reduction in add-on trial
- Safety profile updated with black box warning of risk of PML
- TYSABRI® approved by FDA and EMEA in June 2006 for treatment of MS
- TYSABRI® approved by FDA in January 2008 for treatment of Crohn's Disease
- Risk management plan was a crucial element of the submission required for approval

Timeline



Millions of $$ were lost by Investors

Investors watchfully waiting….
Why so few events post-marketing?

Why only 2 events in 35,000 patients?

- Market Buzz – 1 per 1000 patients on Tysabri will get PML
  - This comes from approximately 2000 patients were treated in MS and 2 patients got PML
- 35,000 patients receiving drug and no PML led to speculation
  - Perhaps there was something different about the patients that got PML in the clinical trials – they were on combination therapy with another agent
  - Maybe the risk is much lower or non-existent when patients are on a single agent
  - Our risk management plan is screening patients so well that we have eliminated the risk

PML in MS – Tysabri® Clinical Experience

- PML with Tysabri® Use in MS
  - 2 cases of PML were observed in 1869 patients with MS treated for a median of 120 weeks (ie, 2.3 years) – *this is taken right from the US label*
    - Observations: 4,300 patient years
    - 2 cases per 4,300 patient years = 0.00046
  - From the clinical experience, we would then expect
    - 4.6 events per 10,000 patient years
    - Or, 1 per 2000 patient years
    - Or, 1 per 1000 patients treated for 2 years
  - Also, patients that had a PML event were treated with concomitant interferon beta-1a therapy with Tysabri®

What is the Risk Model?

- Is it random?
- Other covariates or risk factors?
- Length of exposure?
- Statistical model?

- For example:
  - Model I: Risk does not depend on length of exposure and it is 1 per 1000 patients regardless of length of treatment
    - We have approximately 35,000 patients treated
    - Expected number of events: 35 compared to 2 observed
    - Model I, unlikely

Model II: The risk increases over time, but for any fixed amount of time it is constant.

- For example
  - Risk of dying in a car accident: 45,000 died in a car accident out of 291 MM in the US
    The one year odds are 1 out of 6500 persons per year
    Over a lifetime (78 year expectancy): 78 out of 6500 or 1 out of 83

Risk of Dying from Various *RARE* Events in the US			
Event	Incidence	One Year Risk	Lifetime Risk
Car Accident	45,000	1 out of 6,500	1 out of 83
Airplane Crash	728	1 out of 400,000	1 out of 5,000
Walking across the street	6000	1 out of 48,500	1 out of 625
Drowning	3,306	1 out of 88,000	1 out of 1,100
Lightning	47	1 out of 6.2MM	1 out of 80,000
Tysabri® from Clinical Experience	2	1 out of 4,300 or 0.00046	1 out of 430*

*Median use is 10 years.

PML Risk (Random Patient-Year Exposure Model)

The risk is 4.6 per 10,000 patients per year.

- For example, if 10,000 patients are treated for 6 months, the expected number of events would be 10,000 X 0.5 X 0.00046 or 2.3 events
- Or, if 5,000 patients are treated for 1 year, the expectation is 5,000 X 0.00046 or 2.3 events
- In 2 distinct scenarios, you would expect 2.3 events.

- Given the clinical experience and estimated exposure in the market, what is the risk or expected number of events?

Time	*Exposure (patient years)**	*Expectation 95% Confidence Interval*	*Probability of Observing Zero Events*	*Probability of Observing at most 2 Events*
Q2'2008	25,570	12.68 (5, 20)	0.0000031	0.0003
Q3'2008	36,194	16.65 (8, 23)	0.0000010	0.0000
Q4'2008	46,241	21.27 (12, 30)	0.0000000	0.0000
Q1'2009	57,726	26.55 (16, 37)	0.0000000	0.0000

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Patient-Year Exposure Model

- This model does not align well with the current post-marketing experience.
- Post-marketing experience: 2 events were observed after approximately 38,000 patients had been treated. The total treatment experience at that time was approximately 27,000 person years. This PML event rate is 0.7 per 10,000 patient years. The 95% confidence interval is 0 to 1.8 compared to 4.6 in the clinical experience.
- So, is the post-marketing experience really different from what was observed in the clinic?
- Even though we had 27,000 patient years exposure, only 5000 patients had completed one year. Recall both events in the clinic occurred while on treatment more than 2 years.
- We decided to watch and wait and re-evaluate with new cases and more exposure.

PML in MS -Tysabri® Post-marketing Experience

- As of 30 Nov 2008[1]:

Number of Patients Exposed	42,000
Number of Patient Years	41,000
Number of Patients Exposed for 12+ months	19,000
Number of Patients Exposed for < 12 months	23,000
Number of Patients Exposed for 18+ months	10,000
Number of Patients Exposed for 24+ months	3,700

[1]Numbers are Approximate

PML in MS -Tysabri® Post-marketing Experience

- As of 15 Dec 2008, there had been 4 cases of PML[1]

Overall Incidence	1 per 10,000
Incidence for Patients Exposed for 12+ months	1 per 2,500

[1]Numbers are Approximate

The risk appears to be increasing with the length of exposure

- What is the probability that we would have NO events in the post-marketing experience with less than 12 months exposure?
- Depends on the rate:

Rate Estimated	probability
From Post-Market (1 per 10,000)	0.10
From Clinical Trials (4.6 per 10,000)	< 0.0001

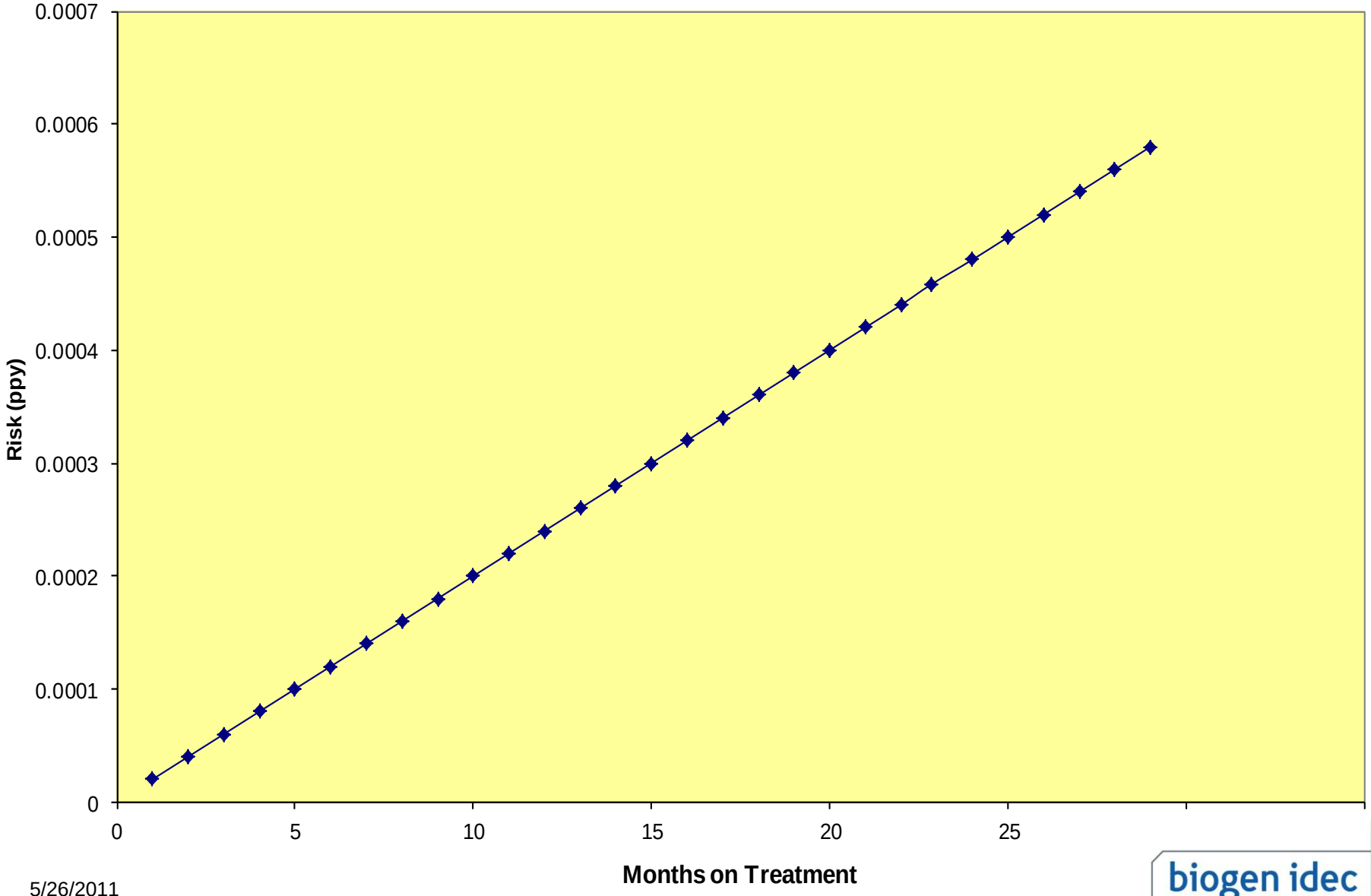
Given the data to date, how can we predict risk ?

- Random Risk Model
  - Risk does not depend on length of exposure, purely binary at 1/1000
  - With 42,000 patients treated, we expect 42 events
  - Observed only 4, unlikely its purely random

- Constant Risk
  - Risk is constant over a period of time, but increases with length of exposure
  - With 46,000 patient years exposure, expected value is 21 events
  - Probability we observe only 4 events is < 0.0001

- Non-random Risk Models
  - Linear Models – Risk increases linearly with each exposure
  - S-curve models – Risk increases according to a sigmoid function

Linear Increase in Risk with Risk = 0.00046 ppy at 2 years.



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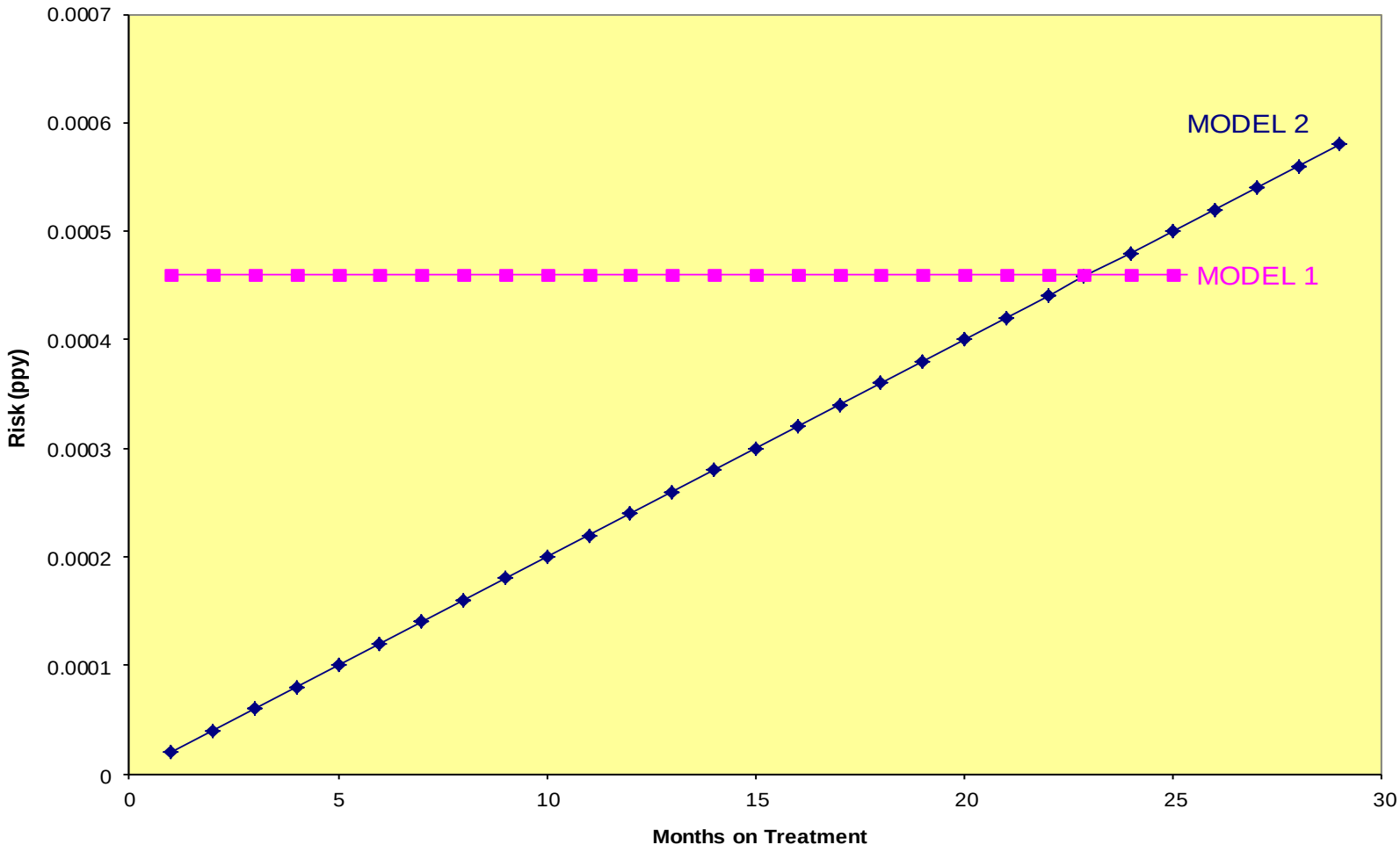
Linear Increase in Risk with Risk = 0.00046 ppy at 2 years versus Risk = 0.00046 ppy for all durations of exposure



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Linear Increase – Risk increases linearly with each monthly infusion and the risk equals 0.00046 ppy at 2 years.

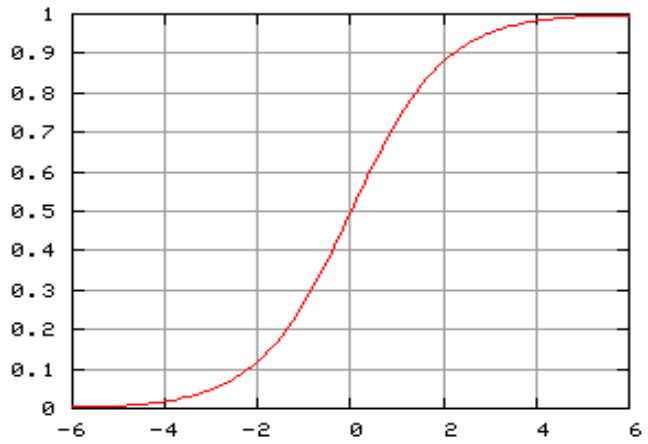
- Given the clinical experience and estimated exposure in the market, what is the risk or expected number of events?

Time	*Exposure (patient years)*	*Expectation 95% Confidence Interval*	*Probability of Observing Zero Events*	*Probability of Observing at most 4 Events*
Q2'08	25,570	7.40 (2, 12)	0.0006	0.0219
Q3'08	36,194	10.81 (4, 17)	0.0000	0.0014
Q4'08	46,241	15.18 (7, 23)	0.0000	0.0000
Q1'09	57,726	20.62 (11, 30)	0.0000	0.0000

Non-random risk models

- Linear
  - Rate increases linearly over time to 4.6 per 10K person years at 2 years
  - This model does not appear to fit the observed risk in the marketed population

- What other models of increasing risk with increasing exposure are plausible?
  - Let's postulate a model where there is very little risk, almost none, until some threshold of exposure and then the risk goes up quickly and remains at a low level because only certain patients may be susceptible, in the first place
  - The Family of S-Curves: The risk of PML is very low at the beginning of treatment, but suppose after some length of time say one year or so, the risk increases rapidly. The risk then reaches an equilibrium rate or threshold because perhaps not everyone will be susceptible to this risk.



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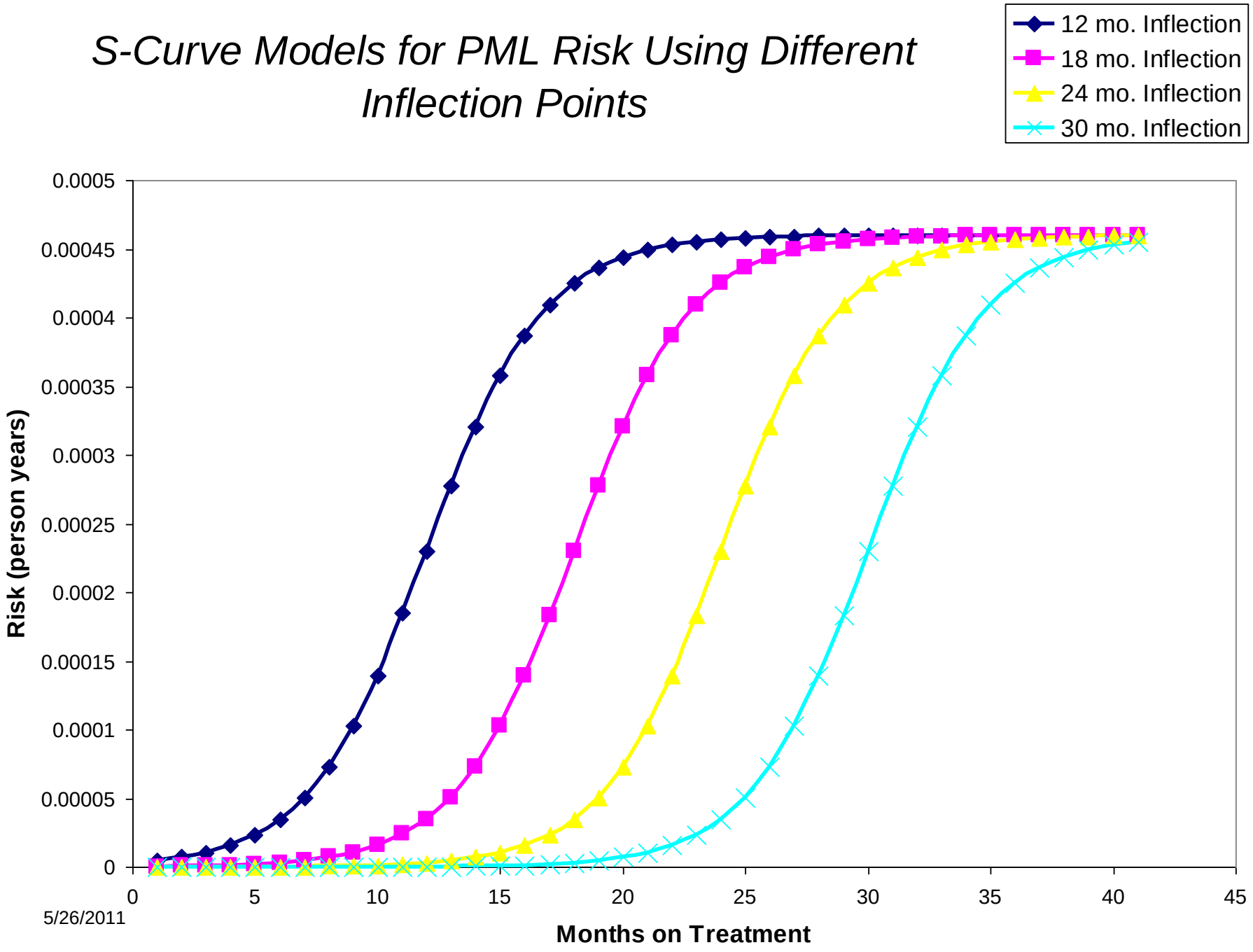
S Curve Models for PML Risk

- Inflection Point is the mid-point of the curve – halfway between 0 and the threshold.

- Three Models
  - Model S1: S-curve with the Inflection Point at 1 year
  - Model S2: S-curve with the Inflection Point at 1.5 years
  - Model S3: S-curve with the Inflection Point at 2 years
  - Model S4: S-curve with the Inflection Point at 2.5 years

- Each model assumes the rate reaches the maximum rate of 4.6 per 10,000 person years at twice the inflection point.

S-Curve Models for PML Risk Using Different Inflection Points



- *Given the current and projected exposure in the market what is the expected number of PML events?*

Model S1 – S-Curve for Risk with Inflection Point at 1 year

Time	*Exposure (patient years)*	*Expectation 95% Confidence Interval*	*Probability of Observing Zero Events*	*Probability of Observing at most 4 Events*
Q4'08	46,241	14.45 (7, 22)	0.0000	0.00129
Q1'09	57,726	19.03 (10, 28)	0.0000	0.00004

Model S2 – S-Curve for Risk with Inflection Point at 1.5 years

Time	*Exposure (patient years)*	*Expectation 95% Confidence Interval*	*Probability of Observing Zero Events*	*Probability of Observing at most 4 Events*
Q4'08	46,241	9.36 (3, 16)	0.0000	0.044
Q1'09	57,726	13.19 (6, 21)	0.0000	0.003

- ***Given the current and projected exposure in the market what is the expectation of the number of PML events?***

Model S3 – S-Curve for Risk with Inflection Point at 2 years

Time	*Exposure (patient years)*	*Expectation 95% Confidence Interval*	*Probability of Observing Zero Events*	*Probability of Observing at most 4 Events*
Q4'08	46,241	4.46 (2, 9)	0.0116	0.540
Q1'09	57,726	7.41 (2, 13)	0.0006	0.139

Model S4 – S-Curve for Risk with Inflection Point at 2.5 years

Time	*Exposure (patient years)*	*Expectation 95% Confidence Interval*	*Probability of Observing Zero Events*	*Probability of Observing at most 4 Events*
Q4'08	46,241	1.05 (0, 3)	0.3510	0.996
Q1'09	57,726	2.61 (0, 6)	0.0737	0.876

Conclusions: S Curve Models with Threshold at 0.00046 risk at 2 years

- Model S1 – Inflection point at 1 year
  - It is unlikely that we would only see 4 events by Q4'08 ($p < 0.0013$.)
- Model S2 – Inflection point at 1.5 years
  - It is unlikely that we would only see 4 events by Q4'08 ($p < 0.044$.)
- Model S3 – Inflection point at 2 years
  - It would be unlikely to see only 4 events by the end of 2008 ($p < 0.54$)
  - By the end of Q1'09, it is more unlikely ($p < 0.003$)
  - We would expect 3 more events by Q1'09 using this model.
- Model S4 – Inflection point at 2.5 years
  - We would not expect to see any events until 2009.

Overall Conclusions in Modeling Exercise

  - Either the duration of exposure matters, or
  - The risk is much lower in the marketed population, or
  - Both !!

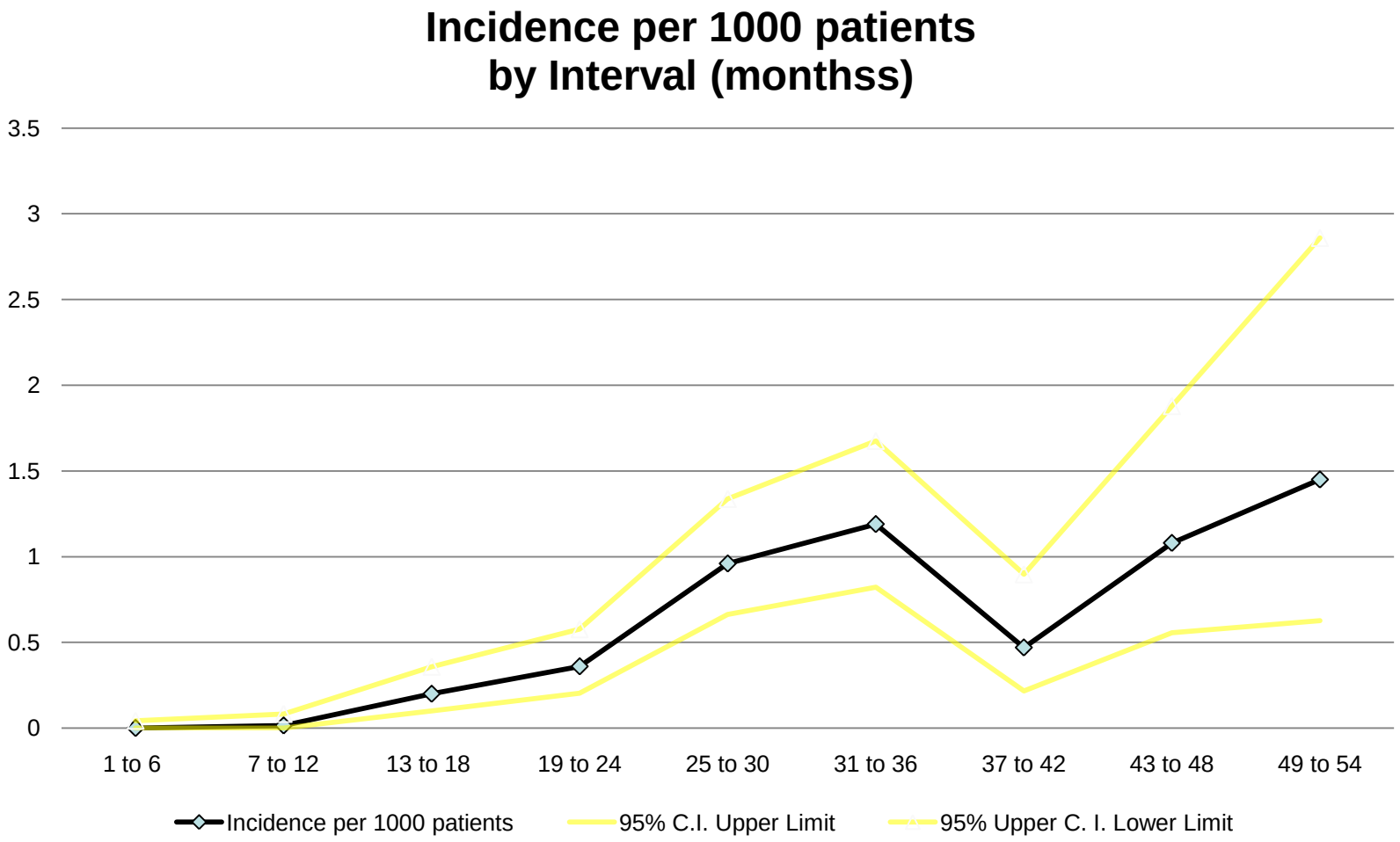
- It also appears the risk of PML does not increase linearly with time.

- If the risk of PML is related to length of exposure in a s-curve relationship, it depends on the inflection point.
  - 1 year – Unlikely, Similar in Likelihood to a Linear Model.
  - 1.5 Years Unlikely.
  - 2 years – Best Fitting Model.
  - 2.5 Years – Unlikely.

- Post-marketing rate is 4 events per 42,000 patient years or 0.9 per 10,000 with a 95% confidence interval of 0 to 1.2 events per 10,000.

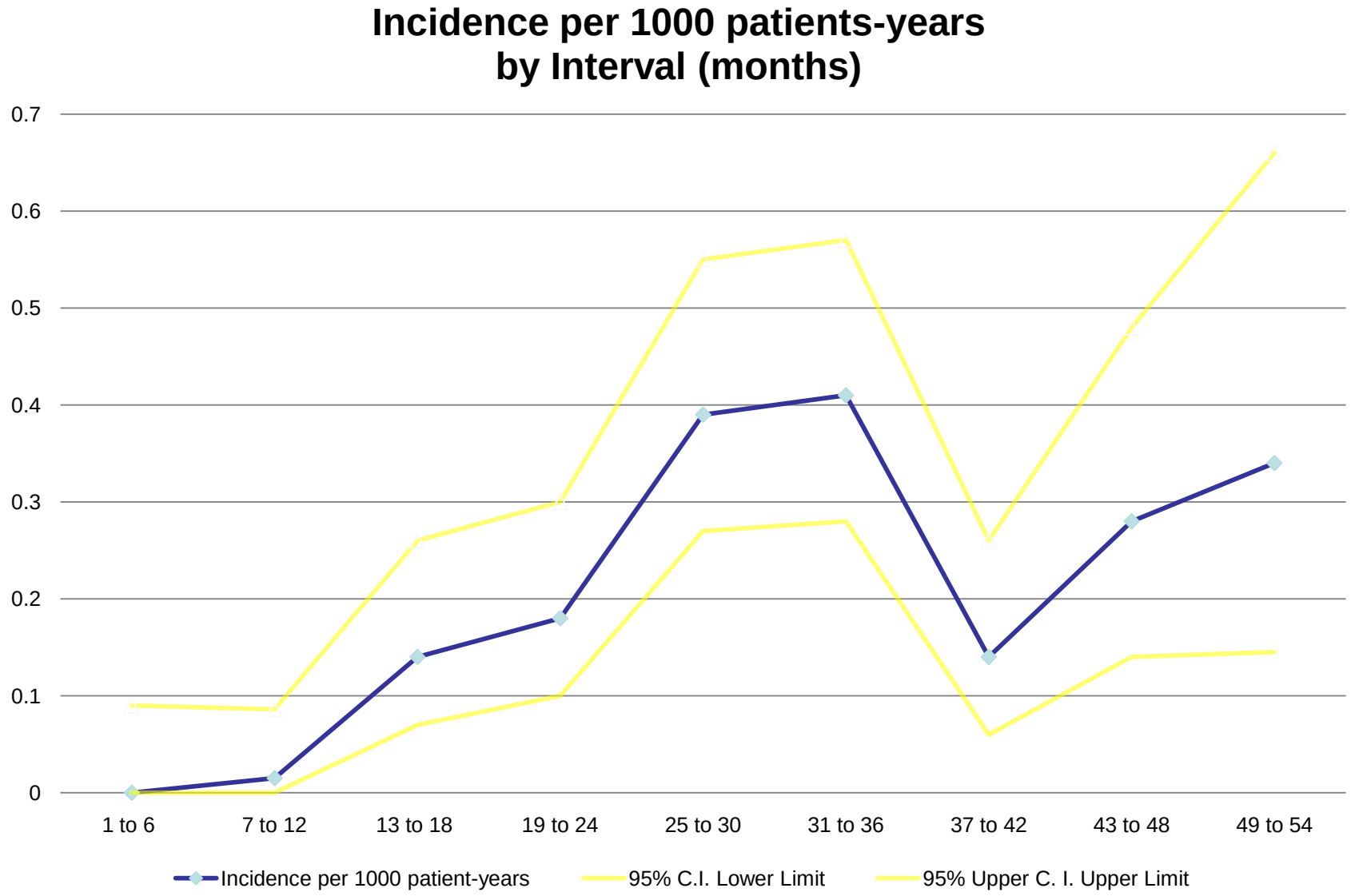
Where are we today – 2 years later with data !!

Interval Exposure (months)	Patients Exposed	PML Events	Incidence per 1000 patients	95% Confidence Interval
1 to 6	86,200	0	0	0.0 to 0.043
7 to 12	67,250	1	0.015	0.0 to 0.083
13 to 18	55,000	11	0.20	0.100 to 0.358
19 to 24	45,000	16	0.36	0.203 to 0.577
25 to 30	35,500	34	0.96	0.663 to 1.337
31 to 36	27,650	33	1.19	0.822 to 1.676
37 to 42	19,000	9	0.47	0.216 to 0.897
43 to 48	11,150	12	1.08	0.556 to 1.879
49 to 54	5,510	8	1.45	0.627 to 2.860
55 to 60	1,830	0	0	0.000 to 2.014
Total	86,196	124	1.44	1.197 to 1.715


Incidence per 1000 patients
by Interval (monthss)
3.5
3
2.5
2
1.5
1
0.5
0
1 to 6
7 to 12
13 to 18
19 to 24
25 to 30
31 to 36
37 to 42
43 to 48
49 to 54
Incidence per 1000 patients
95% C.I. Upper Limit
95% Upper C. I. Lower Limit

Where are we today (in patient-years)

Interval Exposure (months)	Patients Years Exposed	PML Events	Incidence per 1000 patients	95% Confidence Interval
1 to 6	39,127	0	0	0.0 to 0.094
7 to 12	64,544	1	0.015	0.0 to 0.086
13 to 18	80.353	11	0.14	0.068 to 0.245
19 to 24	87,967	16	0.18	0.104 to 0.295
25 to 30	87,083	34	0.39	0.270 to .546
31 to 36	81,257	33	0.41	0.280 to .570
37 to 42	64,885	9	0.14	0.063 to 0.263
43 to 48	43,340	12	0.28	0.143 to 0.484
49 to 54	23,829	8	0.34	0.145 to 0.662
55 to 60	8,611	0	0	0.000 to 0.428
Total	158,278	124	0.783	0.652 to 0.934


Incidence per 1000 patients-years
by Interval (months)
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
1 to 6
7 to 12
13 to 18
19 to 24
25 to 30
31 to 36
37 to 42
43 to 48
49 to 54
Incidence per 1000 patient-years
95% C.I. Lower Limit
95% Upper C. I. Upper Limit

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Lessons Learned

- All eyes are on the next occurrence of an event !!
- Incidence depends on whether its quoted by patient or patient-year
- Occurrence may depend on length of exposure or other co-factors
- Continuous monitoring creates demand for statistical evaluation