Application Examples – Claims Based on Kaplan Meier Analysis

Example: Case 1

Background:

Table 1: Efficacy Results for Study 1 (ITT Population)

	placebo	Product X
Number of Patients	411	402
Overall Survival		
Median (months)	15.6	20.3
95% confidence interval (CI)	14.29-16.99	18.46-24.18
Hazard ratio** (95% CI)		0.66 (0.54; 0.81)
p-value		0.00004

Figure 1: Plot of Kaplan Meier Estimates for Survival

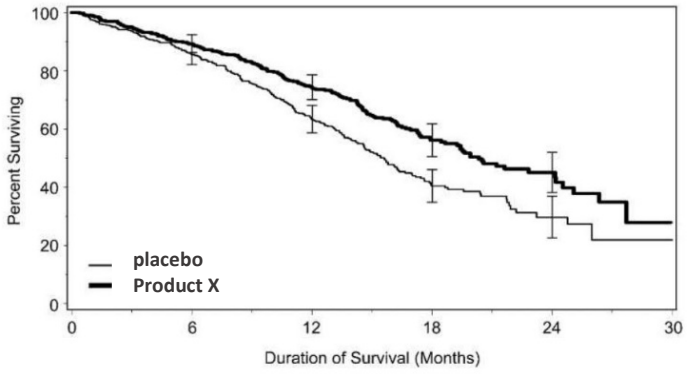
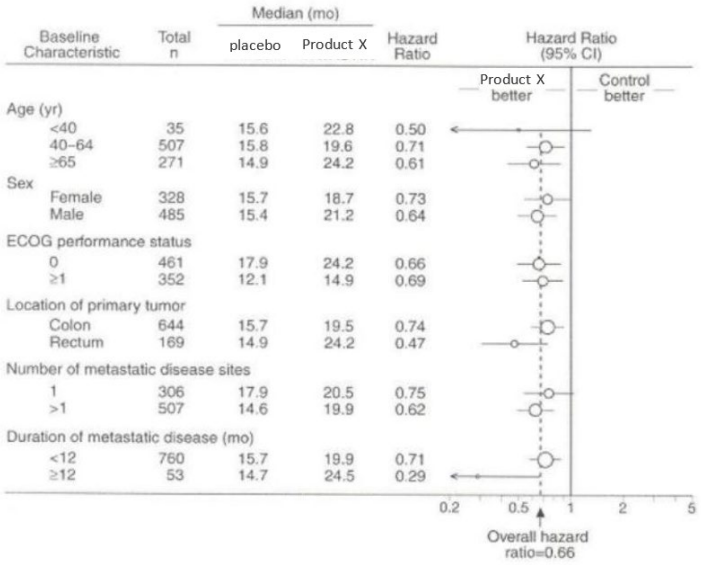


Figure 2: Duration of Survival by Baseline Risk Factor



Claim 1a - risk reduction (valid application until April 2021)

Product X demonstrated superior OS compared with placebo: 34% reduction in risk of death (HR 0.66 [95% CI: 0.54-0.81]; p=0.0004)

Qualification for claim 1a

Based on provision 4, qualify with ONE of the following:

i. KM curve
ii. median time to event:
    - **median time to death: Product X 20.3 months vs. placebo 15.6 months**
iii. timepoint/milestone estimates (these can be obtained from data on file if they are not published in the source)
iv. number of events at endpoint (these can be obtained from data on file if they are not published in the source)

Claim 1b - risk reduction (required application beginning in April 2021)

Product X demonstrated superior OS compared with placebo: 34% reduction in risk of death (HR 0.66 [95% CI: 0.54-0.81]; p=0.0004)

Qualification for claim 1b

As per provision 6, should the client choose to promote claim 1b, it must be qualified with iv above; this applies even if i, ii and iii are present.

An alternative claim (valid application beginning immediately):

Product X demonstrated superior OS compared with placebo: 34% reduction in instantaneous risk of death (HR 0.66 [95% CI: 0.54-0.81]; p=0.0004)

This can be qualified with any one of i, ii, iii and iv above.

Claim 2 – time

Product X significantly delayed time to death vs. placebo (HR 0.66 [95% CI: 0.54-0.81]; p=0.0004)

OR

Product X significantly prolonged time to death vs. placebo (HR 0.66 [95% CI: 0.54-0.81]; p=0.0004)

OR

Product X significantly prolonged overall survival vs. placebo (HR 0.66 [95% CI: 0.54-0.81]; p=0.0004)

Qualification for claim 2

Same qualification as for claim 1.

Acceptable:

Product X significantly delayed time to death vs. placebo (HR 0.66 [95% CI: 0.54-0.81]; p=0.0004)
Median time to death: Product X 20.3 months vs. placebo 15.6 months

Beginning April 2021, the following will NOT be acceptable as per provision 3:

Product X significantly delayed time to death vs. placebo: 20.3 months vs. 15.6 months (HR 0.66 [95% CI: 0.54-0.81]; p=0.0004)

This is because the HR and associated statistics relate to the entire KM curve and not to the specific measurement of mean time to death, which is a single point in time (i.e. when 50% of subjects in each arm experienced the event).

Beginning April 2021, the following will NOT be acceptable as per provision 3:

- **Product X demonstrated 4.7 months increase in median time to death vs. placebo**
- **Product X prolonged time to death by 4.7 months vs. placebo**
- **Product X increased median time to death by 30% vs. placebo**

Claim 3

Promotion of the complete forest plot is acceptable without any additional qualification; it already fulfills provision 4 ii.

Please note that if either of the medians was NR, additional qualification would be required.

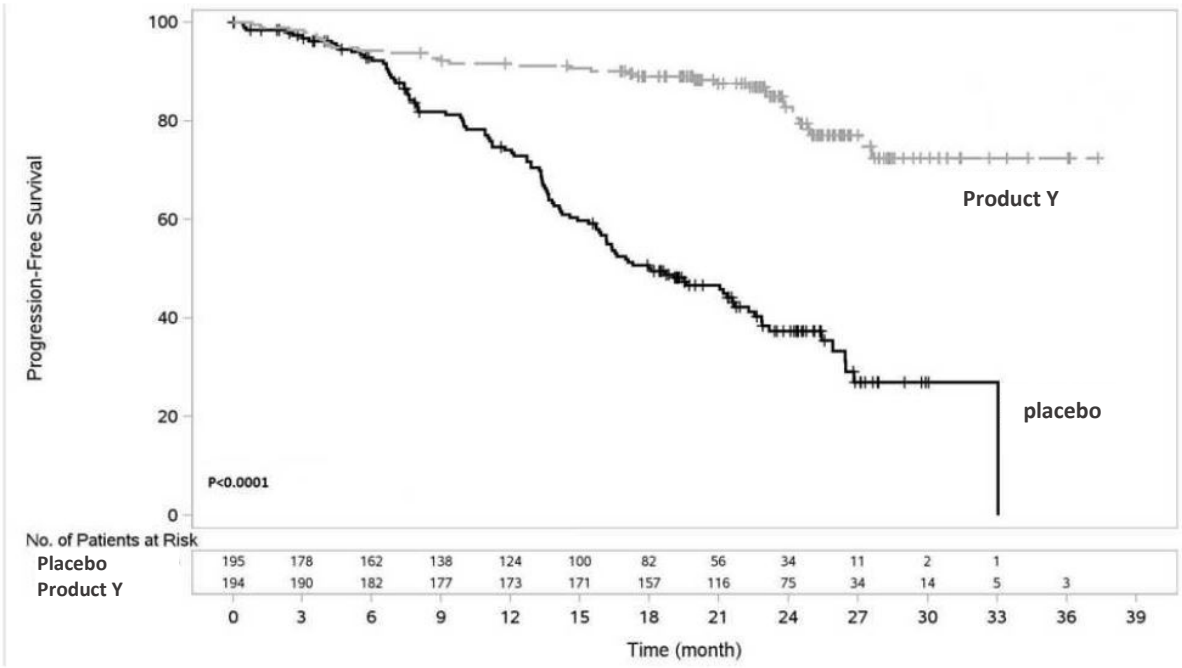
Example: Case 2

Background:

Table 2: Efficacy Results for Study 1 by IRC Assessment (ITT Population)

	Product Y (N = 194)	Placebo (N = 195)
Progression-free survival		
Number of events (%)	35 (18.0)	106 (54.4)
Disease progression	26 (13)	91 (47)
Death events	9 (5)	15 (8)
Median, months, (95% CI)[a]	Not reached	18.1 (15.8, 22.3)
HR (95% CI)[a]	0.19 (0.13, 0.28)	
p-value	p < 0.0001	

Figure 3: Kaplan-Meier Curve of IRC-Assessed Progression-Free Survival (ITT Population)



Claim 1a – risk reduction (valid application until April 2021)

Product Y demonstrated superior PFS compared with placebo: 81% reduction in risk of progression or death vs. placebo (HR: 0.19 [95% CI: 0.13-0.28]; p<0.0001)

Qualification for claim 1a

Based on provision 4, qualify with ONE of the following:

i. KM curve
ii. median time to event is not an option in this case as it was NR in one arm
iii. timepoint/milestone estimates (these can be obtained from data on file if they are not published in the source):
    - **The 2-year rates of PFS for the Product Y and placebo arms were 82.76% (95% CI: 76.62-88.90) and 39.42% (95% CI: 31.03-47.82), respectively (IRC-assessed in the ITT population)**
iv. number of events at endpoint
    - **number of events: Product Y 35/194 vs. placebo 106/195**

Claim 1b - risk reduction (required application beginning in April 2021)

Product Y demonstrated superior PFS compared with placebo: 81% reduction in risk of progression or death vs. placebo (HR: 0.19 [95% CI: 0.13-0.28]; p<0.0001)

Qualification for claim 1b

As per provision 6, should the client choose to promote claim 1b, it must be qualified with iv above; this applies even if i, ii and iii are present.

An alternative claim (valid application beginning immediately):

Product Y demonstrated superior PFS compared with placebo: 81% reduction in instantaneous risk of progression or death vs. placebo (HR: 0.19 [95% CI: 0.13-0.28]; p<0.0001)

This can be qualified with any one of i, ii, iii and iv above.

Example: case 3

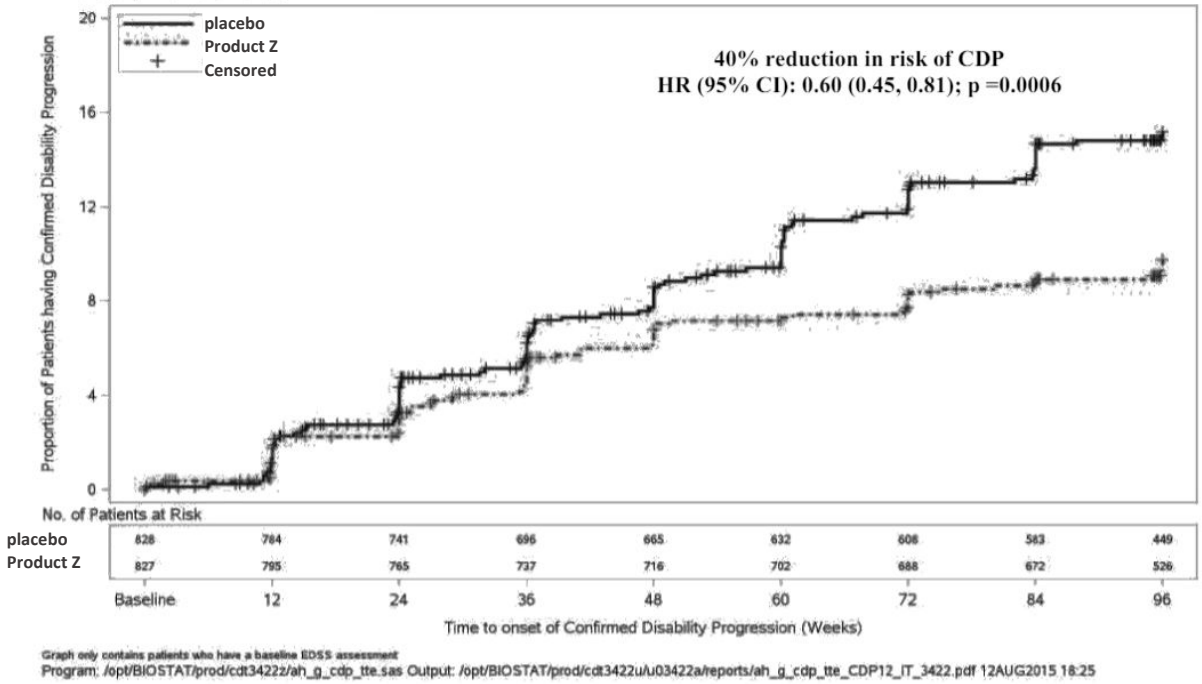
Background:

Table 3: Clinical Endpoints from RRMS Study 1 and RRMS Study 2

Endpoints	**RRMS Study 1**		**RRMS Study 2**	
	Product Z (n=410)	placebo (n=411)	Product Z (n=417)	placebo (n=418)
Clinical Endpoints				
Annualized Relapse Rate (primary endpoint)	0.156	0.292	0.155	0.290
Rate ratio (95% CI) Relative Reduction	0.536 (0.400, 0.719) 46% (p<0.0001)		0.532 (0.397, 0.714) 47% (p<0.0001)	
Proportion of patients with 12 weeks Confirmed Disability Progression	9.8% Product Z vs 15.2% placebo			
Hazard ratio (95% CI) Risk Reduction (Pooled analysis)	0.60 (0.45, 0.81) 40% (p=0.0006)			

Figure 4: Kaplan-Meier Plot of Time to Onset of Confirmed Disability Progression Sustained for at Least 12 Weeks with the Initial Event of Neurological Worsening Occurring during the Double-blind Treatment Period (Pooled ITT Population)*

Pooled: RRMS Studies 1 and 2



**Pre-specified pooled analysis of Study 1 and Study 2*

Claim 1a – risk reduction (valid application until April 2021)

Product Z demonstrated 40% reduction in risk of patients experiencing 12-week confirmed disability progression compared with placebo (HR 0.60 [95% CI: 0.45-0.81]; p=0.0006)

Qualification for claim 1a

Based on provision 4, qualify with ONE of the following:

i. 1-KM curve
ii. median time to event is not an option as it was NR for both arm
iii. timepoint/milestone event rates (these can be obtained from data on file if they are not published in the source)
iv. number of events at endpoint
    - **number of patients: Product Z 80/821 vs. placebo 127/835**

Claim 1b - risk reduction (required application beginning in April 2021)

Product Z demonstrated 40% reduction in risk of patients experiencing 12-week confirmed disability progression compared with placebo (HR 0.60 [95% CI: 0.45-0.81]; p=0.0006)

Qualification for claim 1b

As per provision 6, should the client choose to promote claim 1b, it must be qualified with iv above; this applies even if i, ii and iii are present.

An alternative claim (valid application beginning immediately):

Product Z demonstrated 40% reduction in risk of patients experiencing 12-week confirmed disability progression compared with placebo (HR 0.60 [95% CI: 0.45-0.81]; p=0.0006)

This can be qualified with any one of i, ii, iii and iv above.