Dossier zur Nutzenbewertung gemäß § 35a SGB V

Selumetinib (Koselugo®)

AstraZeneca GmbH

Modul 4A, Anhang 4-G2

Behandlung von symptomatischen, inoperablen plexiformen Neurofibromen bei Kindern ab 3 Jahren und Jugendlichen mit Neurofibromatose Typ 1

Vollständige Darstellung der für das vorliegende Dossier relevanten Ergebnisse als unveränderte Ausgabe der Statistik-Software

Stand: 12.08.2021

Table 1.8.1 Percent change in target PN volume Mean-Difference - Intervention vs. Control
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural Histry Study NF1 age-matched and Tipifarnib

Group	n	Time period, years [a] Mean (95% CI)	PN volume % change / year [b], Mean (95% CI)	Estimated annual PN growth rate Mixed Model [c] Adjusted Mean	95% CI
SPRINT Phase II Stratum I [d]	48	1.8 (1.7, 2.0)	-9.4 (-12.2, -6.5)	-16.9	-20.2, -13.5
Natural History (age-matched) [e]	92	7.2 (6.3, 8.0)	22.9 (17.6, 28.3)	20.5	16.5, 24.5
Tipifarnib [f]	29	1.2 (0.8, 1.6)	27.4 (19.9, 35.0)	NC	NC
Adjusted mean difference (SPRINT vs. N-H)				-37.3	-42.4, -32.2

[a] NH: Time period is defined from the first to the last available MRI assessment or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib. SPRINT: Time period is defined from the baseline MRI assessment date to the last evaluable assessment date up to data cut-off or treatment discontinuation (whichever occurred first). TIPI: Time period is defined from the baseline MRI assessment date to the last evaluable assessment date up. [b] % PN volume change from the first MRI (baseline MRI for SPRINT) to the last MRI assessment over time period in years. [c] Mixed models include PN volume % change as response, time (years), baseline age and baseline PN volume as covariates. NH and TIPI mixed models also contain a quadratic term for time.
[d] Includes patients with baseline and at least one subsequent MRI assessment. [e] Includes patients aged 3 to 18 years with at least one MRI within this age and one subsequent MRI. [f] Includes patients with at least one MRI and one subsequent MRI.
NC = Not Calculable. CI = Confidence interval. PN = Plexiform neurofibromas. NH = Natural History. TIPI = Tipifarnib. FU = Follow-up
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Table 1.8.2 Absolute change in target PN volume Mean-Difference - Intervention vs. Control
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural Histry Study NF1 age-matched and Tipifarnib

Group	n	Time period, years [a] Mean (95% CI)	PN volume change / year [b], Mean (95% CI)	Estimated annual PN growth rate Mixed Model [c] Adjusted Mean	95% CI
SPRINT Phase II Stratum I [d]	48	1.8 (1.7, 2.0)	-116 (-178.5, -52.4)	-89.5	-112.4, -66.6
Natural History (age-matched) [e]	92	7.2 (6.3, 8.0)	97.9 (62.0, 133.8)	NC	NC
Tipifarnib [f]	29	1.2 (0.8, 1.6)	115.9 (39.4, 192.4)	NC	NC
Adjusted mean difference (SPRINT vs. N-H)				NC	NC

[a] NH: Time period is defined from the first to the last available MRI assessment or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib. SPRINT: Time period is defined from the baseline MRI assessment date to the last evaluable assessment date up to data cut-off or treatment discontinuation (whichever occurred first). TIPI: Time period is defined from the baseline MRI assessment date to the last evaluable assessment date up. [b] PN volume change from the first MRI (baseline MRI for SPRINT) to the last MRI assessment over time period in years. [c] Mixed models include PN volume change as response, time (years), baseline age and baseline PN volume as covariates. NH and TIPI mixed models also contain a quadratic term for time. [d] Includes patients with baseline and at least one subsequent MRI assessment. [e] Includes patients aged 3 to 18 years with at least one MRI within this age and one subsequent MRI. [f] Includes patients with at least one MRI and one subsequent MRI.
NC = Not Calculable. CI = Confidence interval. PN = Plexiform neurofibromas. NH = Natural History. TIPI = Tipifarnib. FU = Follow-up
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Table 1.9.1 Percent change in sum of all PN volumes Mean-Difference - Intervention vs. Control
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural Histry Study NF1 age-matched and Tipifarnib

Group	n	Time period, years [a] Mean (95% CI)	PN volume % change / year [b], Mean (95% CI)	Estimated annual PN growth rate Mixed Model [c] Adjusted Mean	95% CI
SPRINT Phase II Stratum I [d]	48	1.8 (1.7, 2.0)	-10.1 (-12.8, -7.4)	-17.5	-20.7, -14.3
Natural History (age-matched) [e]	92	7.2 (6.3, 8.0)	22.9 (17.6, 28.3)	20.5	16.5, 24.5
Tipifarnib [f]	29	1.2 (0.8, 1.6)	32.7 (19.8, 45.6)	NC	NC
Adjusted mean difference (SPRINT vs. N-H)				-38.0	-43.0, -32.9

[a] NH: Time period is defined from the first to the last available MRI assessment or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib. SPRINT: Time period is defined from the baseline MRI assessment date to the last evaluable assessment date up to data cut-off or treatment discontinuation (whichever occurred first). TIPI: Time period is defined from the baseline MRI assessment date to the last evaluable assessment date up. [b] % PN volume change from the first MRI (baseline MRI for SPRINT) to the last MRI assessment over time period in years. [c] Mixed models include PN volume % change as response, time (years), baseline age and baseline PN volume as covariates. NH and TIPI mixed models also contain a quadratic term for time.
[d] Includes patients with baseline and at least one subsequent MRI assessment. [e] Includes patients aged 3 to 18 years with at least one MRI within this age and one subsequent MRI. [f] Includes patients with at least one MRI and one subsequent MRI.
NC = Not Calculable. CI = Confidence interval. PN = Plexiform neurofibromas. NH = Natural History. TIPI = Tipifarnib. FU = Follow-up
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Table 1.9.2 Absolute change in sum of all PN volumes Mean-Difference - Intervention vs. Control
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural Histry Study NF1 age-matched and Tipifarnib

Group	n	Time period, years [a] Mean (95% CI)	PN volume change / year [b], Mean (95% CI)	Estimated annual PN growth rate Mixed Model [c] Adjusted Mean	95% CI
SPRINT Phase II Stratum I [d]	48	1.8 (1.7, 2.0)	-128 (-195.1, -61.7)	-99.5	-130.3, -68.8
Natural History (age-matched) [e]	92	7.2 (6.3, 8.0)	97.9 (62.0, 133.8)	NC	NC
Tipifarnib [f]	29	1.2 (0.8, 1.6)	142.5 (65.7, 219.4)	NC	NC
Adjusted mean difference (SPRINT vs. N-H)				NC	NC

[a] NH: Time period is defined from the first to the last available MRI assessment or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib. SPRINT: Time period is defined from the baseline MRI assessment date to the last evaluable assessment date up to data cut-off or treatment discontinuation (whichever occurred first). TIPI: Time period is defined from the baseline MRI assessment date to the last evaluable assessment date up. [b] PN volume change from the first MRI (baseline MRI for SPRINT) to the last MRI assessment over time period in years. [c] Mixed models include PN volume change as response, time (years), baseline age and baseline PN volume as covariates. NH and TIPI mixed models also contain a quadratic term for time. [d] Includes patients with baseline and at least one subsequent MRI assessment. [e] Includes patients aged 3 to 18 years with at least one MRI within this age and one subsequent MRI. [f] Includes patients with at least one MRI and one subsequent MRI.
NC = Not Calculable. CI = Confidence interval. PN = Plexiform neurofibromas. NH = Natural History. TIPI = Tipifarnib. FU = Follow-up
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Table 1.13.1 Median Progression-free Survival (PFS) - Overall
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
50	3 (6.0)	NE (NE, NE)	75	56 (74.7)	1.7 (1.4, 2.5)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.1.1 Median Progression-free Survival (PFS) - Gender = Male
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
30	2 (6.7)	NE (NE, NE)	48	38 (79.2)	1.7 (1.3, 2.1)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.1.2 Median Progression-free Survival (PFS) - Gender = Female
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
20	1 (5.0)	NE (NE, NE)	27	18 (66.7)	2.3 (0.9, 4.6)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.1.3 Median Progression-free Survival (PFS) - PN status at enrollment = Progressive
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
21	3 (14.3)	NE (NE, NE)	25	21 (84.0)	1.2 (0.9, 1.5)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.1.4 Median Progression-free Survival (PFS) - PN status at enrollment = Non-progressive
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
15	0	NE (NE, NE)	42	29 (69.0)	2.6 (1.5, 4.6)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.1.5 Median Progression-free Survival (PFS) - PN status at enrollment = Unknown
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
14	0	NE (NE, NE)	8	6 (75.0)	1.6 (0.5,13.7)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.2 Median Progression-free Survival (PFS) weighting by the stabilized weights - Overall
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
52	3 (5.8)	NE (NE, NE)	73	55 (75.3)	1.6 (1.3, 2.1)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.2.1 Median Progression-free Survival (PFS) weighting by the stabilized weights - Gender = Male
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
30	2 (6.7)	NE (NE, NE)	45	36 (80.0)	1.6 (1.2, 2.1)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.2.2 Median Progression-free Survival (PFS) weighting by the stabilized weights - Gender = Female
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
22	1 (4.5)	NE (NE, NE)	28	19 (67.9)	1.5 (0.7, 4.6)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.2.3 Median Progression-free Survival (PFS) weighting by the stabilized weights - PN status at enrol.= Progressive
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
19	3 (15.8)	NE (NE, NE)	28	23 (82.1)	1.2 (0.9, 1.5)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.2.4 Median Progression-free Survival (PFS) weighting by the stabilized weights - PN status at enrol.= Non-progr.
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
24	0	NE (NE, NE)	34	24 (70.6)	2.5 (1.5, 4.6)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.2.5 Median Progression-free Survival (PFS) weighting by the stabilized weights - PN status at enrol.= Unknown
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
8	0	NE (NE, NE)	11	8 (72.7)	1.6 (0.5,13.7)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.3 Median Progression-free Survival (PFS) post 1:1 matching - Overall
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
37	3 (8.1)	NE (NE, NE)	37	27 (73.0)	1.7 (1.2, 2.8)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.3.1 Median Progression-free Survival (PFS) post 1:1 matching - Gender = Male
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
22	2 (9.1)	NE (NE, NE)	23	19 (82.6)	1.8 (1.0, 3.9)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.3.2 Median Progression-free Survival (PFS) post 1:1 matching - Gender = Female
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
15	1 (6.7)	NE (NE, NE)	14	8 (57.1)	1.5 (0.6, NE)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.3.3 Median Progression-free Survival (PFS) post 1:1 matching - PN status at enrollment = Progressive
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
18	3 (16.7)	NE (NE, NE)	15	11 (73.3)	1.4 (0.6, 2.8)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.3.4 Median Progression-free Survival (PFS) post 1:1 matching - PN status at enrollment = Non-progressive
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
15	0	NE (NE, NE)	15	11 (73.3)	1.9 (0.7, 4.1)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.3.5 Median Progression-free Survival (PFS) post 1:1 matching - PN status at enrollment = Unknown
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
4	0	NE (NE, NE)	7	5 (71.4)	2.0 (0.5,13.7)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.4 Median Progression-free Survival (PFS) post 1:2 matching with replacement - Overall
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
46	3 (6.5)	NE (NE, NE)	43	33 (76.7)	2.0 (1.5, 2.1)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.4.1 Median Progression-free Survival (PFS) post 1:2 matching with replacement - Gender = Male
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
27	2 (7.4)	NE (NE, NE)	29	26 (89.7)	2.0 (1.4, 2.0)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.4.2 Median Progression-free Survival (PFS) post 1:2 matching with replacement - Gender = Female
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
19	1 (5.3)	NE (NE, NE)	14	7 (50.0)	2.8 (1.2, NE)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.4.3 Median Progression-free Survival (PFS) post 1:2 matching with replacement - PN status at enrol. = Progressive
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
21	3 (14.3)	NE (NE, NE)	20	16 (80.0)	1.5 (1.2, 4.1)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.4.4 Median Progression-free Survival (PFS) post 1:2 matching with replacement - PN status at enrol. = Non-progr.
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
15	0	NE (NE, NE)	13	8 (61.5)	2.1 (1.4, 5.9)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.

Table 1.13.4.5 Median Progression-free Survival (PFS) post 1:2 matching with replacement - PN status at enrollment = Unknown
SPRINT Phase II Stratum 1, Data cut-off: 29th June 2018, Natural History Data as of 19th Feb 2019

SPRINT			NH		
n	Number (%) of patients with events	Median time (95% CI) (years)	n	Number (%) of patients with events	Median time (95% CI) (years)
10	0	NE (NE, NE)	11	8 (72.7)	2.0 (1.6, 2.0)

SPRINT: PFS is defined as the time from study treatment initiation to the pre-cycle of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last evaluable MRI assessment. PFS in cycles converted to years: No. of cycles * 28/ 365.25.
NH: PFS is defined as the time from first MRI assessment to the date of documented progression or death in the absence of disease progression. Patients not known to have progressed or died at the time of analysis are censored at the last available MRI assessment date or last MRI assessment date prior to the first use of a MEK inhibitor including Selumetinib.