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Development Update

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CONDITIONAL APPROVAL OF MASITINIB IN ALS WITH EMA

The CHMP confirmed that the safety of masitinib is deemed acceptable

CHMP Latest Assessment Report

Conclusion on clinical safety	*"Having considered the data from masitinib studies, the safety profile of mentioned medicinal product is considered acceptable";*

However, the CHMP was not able to conclude on a favorable benefit due to the following methodological issues

Topic		Objection
# 1	**GCP Issues**	Identified GCP deviations to the protocol cannot be corrected retrospectively
# 2	**Primary population without fast progressors**	Significant effect was not demonstrated in the total study population (Normal + Fast progressors) and exclusion of fast progressors from the primary population is not supported
# 3	**Handling of Missing Data with Jump to Reference (J2R)**	Imputation of a penalty for missing data (jump to reference) should be applied to all discontinuations occurring in the masitinib treatment arm
# 4	**Subgroup identified**	New target population is identified post-hoc

As per guideline, impact analyses of all findings that could not be corrected were performed and showed no impact

Guidance (EMA/868942/2011) Framework

	Inspections findings	**Action taken**
Inspection findings which are **likely to influence** the benefit-risk evaluation	• *Deficiencies in blinding of study medication* • *Deficiencies in randomization* • *Violation of diagnostic inclusion- and exclusion criteria* • *Missing source documentation* • *Faults in data management, statistical programming and analyses* • *Fraud and other scientific misconduct*	*No deficiencies*
	• Violation of procedures related to the assessment of the primary efficacy endpoint	Analysis which does not identify any impact on efficacy
	• Inadequate reporting of adverse events and other safety endpoints	Safety : corrected and processes improved
Inspection findings which **may influence** the benefit-risk evaluation	• *Violation of study procedures regarding rescue medication* • *Inadequate calibration of instruments, equipment etc. related to efficacy assessment* • *Rounding issues* • *Failure to document pre-specification of analyses prior to breaking study blind* • *Deficiencies in storage of study medication*	*No deficiencies*
	• Violation of inclusion and exclusion criteria (other than diagnostic criteria)	Analysis which does not identify any impact on efficacy/safety
	• Deviations from protocol-specified visit windows	Rules defined by DSMB shows no impact
	• Discrepancies between the clinical study report and the actual conduct of the study	New CSR Version was released with final actual data
	• Deficiencies in preparation and administration of study medication at investigational sites	One underdosed error in 42% of study patients. No impact

As per guideline, the benefit-risk remains evaluable because critical data from study AB10015 are reliable

Primary efficacy data are reliable

- Raters were experienced in ALSFRS-R scale according to inspectors
- Inspection recorded few discrepancies in ALSFRS-R, which proves it was not systematic
  - Findings in 3 (1.8%) out of 168 patients inspected (43% of study)
  - Finding in 1 out of 4 sites inspected*
- Nevertheless, the ALSFRS-R data have been reassessed at source by independent certified raters and there was no impact

Safety data were deemed acceptable

- The safety profile of masitinib is already considered acceptable by the CHMP

Deviations on other study data have no impact

- Eligibility criteria, riluzole dosing, masitinib dosing, visit windows were investigated
- Impact analysis showed no impact of these deviations, favouring masitinib or modifying study outcome

- **Guidance recommendations are fulfilled** (1)
  - In **superiority studies**, […], inspection findings merely indicating increased variability and **not introducing bias favouring one treatment over the other are relatively unproblematic** in the interpretation of the study results
  - It is important to assess whether the **findings affect** the interpretation of **the primary efficacy endpoint or important safety endpoints**
- **Benefit risk can be evaluated**

(1) 19 September 2012 EMA/868942/2011. Good Clinical Practice Inspectors Working Group (GCP IWG). Chapter 2. General Notes on Findings

There is a necessity in ALS drug development to use a more homogenous population with greater chance to reach week 48 and minimize missing data, justifying the exclusion of Fast Progressors

- Excluding the Fast Progressors from primary analysis was necessary
  - In pivotal studies, there is a need to select a more homogeneous population
  - For a 48-week study in ALS, there is a need to minimize missing data via patient selection criteria

AB10015 – Discontinuation rate at week 48 according to patient status

Patient Status (ΔFS)	Placebo	M4.5
Normal	26.5%	30.5%
Fast	**52.6%**	**56.5%**

- Clinical relevance of the predefined 1.1 points/month cut-off for post-onset ΔFS was based on data published prior to initiation of study AB10015 [1]
- ΔFS has been recognized in many publications as a robust prognostic factor for survival [2]
- Importantly, post-onset (early) ΔFS has been shown to be the clinical determinant of greatest prognostic importance, while other calculations of ΔFS (post-randomization) showed no prognostic value [Requardt 2021].
- The ΔFS from onset of symptoms has been widely used as a selection criteria in recent clinical trial, including for pivotal studies of edaravone and tofersen
- The ΔFS from onset of symptoms is now recognized by the community as a common tool used in clinical practice [3]
- The risk of patient misclassification due to recollection error of first symptom onset is low according to AB10015 data (recall of month of symptom onset is sufficient for correct classification of 98% of patients) and study was successful from a cut of 0.8 to 1.4

[1] [Kollewe K, J Neurol Sci 2008 ;
[2] [Kollewe K, J Neurol Sci 2008 ; Hannaford A, Muscle Nerve. 2023 ; Requardt MV, J Clin Med. 2021 ; Kjældgaard AL, BMC Neurol. 2021 ; Su WM, EBioMedicine. 2021 ; Labra J, J Neurol Neurosurg Psychiatry. 2016 ; Kimura F, Neurology 2006
[3] Ludolph A; Muscle Nerve. 2024

Primary analysis: The definition of discontinuation reasons on which to apply a penalty (called jump to reference) is conventional and alternative methods recommended by EMA were positive

- **Reasons for discontinuation were documented in the eCRF and classification MNAR versus MAR was prespecified in the SAP before unblinding**

- **Jump to Reference (J2R) was not narrow but conventional**
  - J2R was conventional with penalty applied to discontinuations for toxicity and lack of efficacy, and was positive (p=0,0389)
  - J2R applied to discontinuations for toxicity, lack of efficacy and travel was positive (p=0,0376)
  - J2R for all discontinuations is extreme [Carpenter 2013] and close to statistical significance (p=0.0678)
- **First alternative method recommended by EMA was positive :** Tipping-point for penalty on all discontinuations
  - 76%, meaning that 24% of masitinib effect is enough to become significant
  - 76% is "*within what would be empirically expected*" according to Rapporteur (EMEA/H/C/4398, D180 JAR)
- **Second alternative method recommended by EMA was positive : Copy Increment in Reference (CIR)**
  - Was originally recommended by the CHMP (EMEA/H/C/4398, D150 JAR)
  - Was considered acceptable in other ALS EPAR (EMA/CHMP/487533/2023)
  - positive (p=0.0477)

Analysis	Difference, [95% CI]	p-value
J2R Lack of Efficacy/ any AE	2.8 [0.15; 5.46]	0.0389
J2R Lack of Efficacy/ any AE/Travel	2.82 [0.16; 5.48]	0.0376
J2R All discontinuations	2.31 [-0.17; 4.80]	0.0678
Tipping-Point Analysis = 76%	2.48 [0.00; 4.96]	0.0498
CIR	2.67 [0.03; 5.32]	0.0477

There was a benefit on quality of life, as measured by ALSAQ-40 based on a non LOCF method and a trend of benefit on CAFS, although the study was not powered to demonstrate efficacy on CAFS

Significant ALSAQ-40 benefit based on conservative imputation methods

Masitinib 4.5 mg/kg/day – Normal Progressors - ALSAQ-40

Analysis	Difference, [95% CI]	p-value
Multiple Imputation	-7.27 [-13.18; -1.37]	0.0161
Multiple Imputation with J2R	-5.99 [-11.55;-0.44]	0.0343
CIR	-6.04 [-11.51;-0.57]	0.0305

CAFS is close to significance with p-value = 0.07, even though the study was not designed for CAFS as a primary endpoint

Masitinib 4.5 mg/kg/day – Normal Progressors - CAFS analysis

Treatment group	N	Mean Score	Difference of means	p-value
Placebo	113	100.77	14.95	0.0776
Masitinib 4.5	105	115.72		

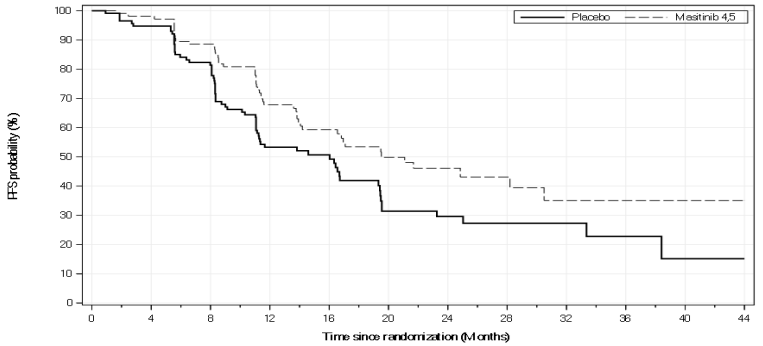
Time to event PFS or EFS, accounting for tracheostomy ventilation and gastrostomy, showed a significant benefit in favour of masitinib

Progression Free Survival was prespecified

There was a significant PFS benefit (+4 months) with a p=0.0159

Masitinib 4.5 mg/kg/day – Normal Progressors. PFS analysis

Treatment group	N	Median months [95% CI]	Wilcoxon p-value
Placebo	113	16 [11; 19]	0.0159
Masitinib 4.5	105	20 [14; 30]	



PFS is robust since all tracheostomy and most of the ventilation or gastrostomy events occurred after progression

Summary of interventions with respect to time of progression

Event Type	Treatment	Total(n)	Before Progression (%)	After Progression (%)
Tracheostomy	Placebo (N=114)	5	0%	100.0%
	Masitinib 4.5 (N=106)	11	0%	100.0%
Ventilator	Placebo (N=114)	21	0%	100.0%
	Masitinib 4.5 (N=106)	24	8.3%	91.7%
Gastrostomy	Placebo (N=114)	20	15.0%	85.0%
	Masitinib 4.5 (N=106)	22	27.3%	72.7%

Event Free Survival (EFS), defined as the earliest between progression, tracheostomy, ventilation, gastrostomy, or death event, remained statistically significant (p=0.01), showing a median benefit of +3 months

Masitinib 4.5 mg/kg/day – Normal Progressors. Analysis of PTVGFS

Treatment group	N	Median months [95% CI]	Wilcoxon p-value
Placebo	113	11 [10; 17]	0.0162
Masitinib 4.5	105	14 [12; 20]	

PTVGFS: Progression Tracheostomy Ventilation Gastrostomy Free Survival

There was a trend of +6 months increase in median overall survival (OS)

As requested by the Rapporteur, new long-term OS analysis was performed, censoring placebo patients at the time they switched to masitinib treatment in the NPP program

This retreatment is essential because OS was significantly improved for placebo patients who switched to masitinib 4.5 mg/kg/day as compared with placebo patients who did not switch

Analysis of overall survival in the NPP program
(placebo switch vs no switch to masitinib)

Treatment group	N	Median months [95% CI]	Wilcoxon p-value
Placebo who did not switch	53	62 [49; NE]	0.0367
Placebo who switched to Masitinib 4.5	25	69 [44; NE]	

With the above mentioned retreatment, there was a trend in overall survival improvement (+6 months) with a p-value of 0.0761

Masitinib 4.5 mg/kg/day – Normal Progressors. OS analysis from baseline
(censoring of placebo patients at time of switch to masitinib - ITT)

Treatment group	N	Median months [95% CI]	Wilcoxon p-value
Placebo	114	40 [30; 49]	0.0761
Masitinib 4.5	106	46 [33; 69]	

EMA guidance (EMA/CHMP/539146/2013) on subgroup applies even to post-hoc analyses

EMA guidance applies to post-hoc analyses initiated by the Applicant

*"[…] it is of interest to **identify post-hoc** a subgroup, where efficacy and risk-benefit is convincing".*

subgroup analysis applies " […] irrespective of whether it is the company or the regulator that is specifying additional investigations of interest".

Scenario 2 of the guidance is applicable because there is a bias in a subset of patients

- The clinical data are statistically persuasive in the primary analysis population
- But there are risks and uncertainties present in a subset of the population, **because there is a bias in this subset**
- Therefore, it might be of interest to identify a subgroup that has not been pre-specified as part of the confirmatory testing strategy, where efficacy and risk-benefit would be convincing

There was a disbalance in a subset of the study population (patients with complete loss of function in at least one individual component of the ALSFRS-R) because ALSFRS-R score was minimized but not stratified by category of severity

A greater proportion of patients with any complete loss of function were randomized in the masitinib arm (20%) as compared with the control arm (8%)

Distribution of patients with complete loss of function in at least one individual component of the ALSFRS-R in the primary analysis population

Normal Progressor	Placebo N=113	Masitinib 4.5 mg/kg/d N=105
ALS with complete loss of function in any individual component of the ALSFRS-R (score of zero on any item)	**8.0%**	**20.0%**

The disease severity in patients with any complete loss of function was higher in the masitinib arm

Population	Stat	Placebo	Masitinib 4.5 mg/kg/d
1 item with score 0	n [Q]	8 [8]	10 [10]
2 items with score 0	n [Q]	0	7 [10]
3 items with score 0	n [Q]	0	3 [9]
4 items with score 0	n [Q]	1 [4]	1 [4]
Total	*n [Q]*	*9 [12]*	*21 [33]*

The bracketed [Q] represents the number of items with a 0-score. Some patients (n) had a 0-score (Q) in more than one item

The treatment effect in the subgroup "*prior to any complete loss of function*" is exceptionally strong, and remains strong when considering both Normal and Fast Progressors

Differential treatment effect (M4.5 vs placebo)		Primary analysis population (Normal Progressors)	Subgroup 'Prior to any complete loss of function' (Normal Progressors)	Subgroup 'Prior to any complete loss of function' (Normal + Fast Progressors)
ΔALSFRS-R (CIR)	Diff. of mean	2.68	3.13	2.76
	p-value	0.0462	0.0308	0.0538
CAFS	Relative benefit	14.8%	20.2%	18.4%
	P-value	0.0776	0.0290	0.0346
ALSAQ-40 (CIR)	Diff. of mean	-6.04	-6.22	-6.74
	p-value	0.0305	0.044	0.0235
FVC (CIR)	Diff. of mean	5.85	7.59	7.79
	p-value	0.0931	0.0384	0.0369
Median PFS	Gain	+ 4 months	+ 9 months	+ 5 months
	Median [95% CI]	20 [14; 30] vs 16 [11; 19]	25 [17; NE] vs 16 [11; 19]	20 [14; 30] vs 15 [11; 19]
	p-value log rank	0.0159	0.0057	0.0183
Median OS (Long-term) (censoring of placebo at time of switch to masitinib)	Gain	+ 6 months	+ 12 months	+ 8 months
	Median [95% CI]	46 [33; 69] vs 40 [30; 49]	53 [36; NE] vs 41 [30; 54]	46 [30; 69] vs 38 [29; 49]
	p-value log rank	0.0761	0.0192	0.0684

- **Clinical data from the subgroup are exceptionally strong due to the consistency and magnitude of effect across endpoints**
- **12 months survival benefit cannot be disregarded**

Next step

AB Science will liaise with the EMA to define the appropriate pathway to registration

- AB Science has the option to request a re-examination
- Re-examination is assessed by new Rapporteur and new Co-Rapporteur
- The re-examination provides the possibility of a Scientific Advisory Group) that can give recommendations on key points
- Key points could include
    - Application of EMA guideline on the GCP
    - Application of EMA guideline on subgroup
    - Application of the two recommendations for handling of missing data
    - Whether excluding Fast progressors from primary analysis is justified

CONDITIONAL APPROVAL OF MASITINIB IN ALS WITH HEALTH CANADA

Clinical objections raised by Health Canada were slightly different from the ones raised by EMA

	Resolved Issue	Pending Issue	Argumentation
Primary analysis population	▪ Changing from phase 2 to phase 3 ▪ Amendments may be an inevitable and were not data-driven ▪ There may be a need to limit heterogeneity ▪ Post-onset decline of 1.1 point per month may be relevant	▪ Amendments were late and not sufficiently justified	▪ Amendment entirely blinded and sufficiently early ○ Implemented 2.5 years prior to study completion ○ Only 8 Fast progressors across 3 treatment arms could have reached the study's primary analysis timepoint ○ When removing the 12% of Normal progressors that could have reached the study timepoint, the study remains positive ○ Study was positive at interim analysis in Normal + Fast ▪ Need to minimize expected high missing data due to discontinuations from Fast progressors with a long time-point of 48-weeks
Statistical method for imputation of missing data in primary analysis	▪ The non-linearity of the distribution of the ALSFRS-R data of the primary analysis (ANCOVA test) was resolved by the positive pre-specified rerandomization test	▪ Missing data have been treated in the planned primary and sensitivity analyses with LOCF, potentially creating a bias in favor of treatment	▪ Sensitivity analysis of the primary analysis based on non LOCF recognized methods are successful and convergent ▪ CAFS endpoint, incorrectly assumed by the Agency to be based on LOCF methodology, whereas it is not, approached the conventionally statistically significant outcome of 5% (p=0.0776), even though the study was not powered for this secondary endpoint.
Subgroup analysis		**Pending Issue** ▪ New proposed claim in patients prior to any loss of function is considered post hoc	**Argumentation** ▪ EMA guidance applies to post-hoc analyses initiated by the Applicant *"[…] it is of interest to **identify post-hoc** a subgroup, where efficacy and risk-benefit is convincing".*

Available preclinical and clinical data in the context of a full approval

Conditional approval raises the question of an approval with a single study that requires very compelling evidences.

Available data from masitinib program are robust and will support full approval, provided a confirmatory study is positive

Preclinical data

- Masitinib has a validated mechanism of action, targeting the innate immune system, via modulation of mast cells and microglia
- Masitinib exerts a protective effect on the **central nervous system**
  - Reduction of microgliosis and aberrant glial cells through CSF-1R inhibition
  - Masitinib prevents motor neuron degeneration
  - Masitinib treatment significantly prolonged survival in post-paralytic SOD1G^{93A} rats
- Masitinib exerts a protective effect on the **peripheral nervous system**
  - Mast cells are immune cells that regulate inflammation. Upon activation they release many proinflammatory mediators.
  - Mast cell infiltration and degranulation contribute to neuromuscular pathology in post-paralytic SOD1^{G93A} rats
  - Masitinib-induced mast cell inhibition significantly reduced rate of neuromuscular junction (NMJ) and motor deficits
- Masitinib has demonstrated ability to lower blood levels of neurofilament light (NfL) in a neurodegenerative disease model (EAE model)

Clinical data

- Study AB10015 is a 48-week study, which is a stronger evidence than a 24-week study, and is same time point as the confirmatory study
- Study AB10015 demonstrated a significant treatment effect
- Data are exceptionally strong in the population close to the confirmatory study and that could be the claim
  - Significant benefit on functional score
  - Significant benefit on quality of life
  - Significant benefit on long-term overall survival

Differential treatment effect (M4.5 vs placebo)		Subgroup 'Prior to any complete loss of function' (Normal Progressors)
ΔALSFRS-R (CIR Analysis)	Diff. of mean	3.13
	p-value	0.0308
CAFS	Relative benefit	20.2%
	P-value	0.0290
ALSAQ-40 (CIR Analysis)	Diff. of mean	-6.22
	p-value	0.044
FVC (CIR Analysis)	Diff. of mean	7.59
	p-value	0.0384
Median PFS	Gain	+ 9 months
	Median [95% CI]	25 [17; NE] vs 16 [11; 19]
	p-value log rank	0.0057
Median OS (Long-term) (censoring of placebo at time of switch to masitinib)	Gain	+ 12 months
	Median [95% CI]	53 [36; NE] vs 41 [30; 54]
	p-value log rank	0.0192