Multicentric pilot study for the treatment of medulloblastoma in adults – the NOA-07 trial

Development Safety Update Report #4

Investigational drugs: Cisplatin, Vincristine and Lomustine in combination with standard treatment (postoperative radiotherapy)

Period covered: 13/Oct/2017 –12/Oct/2018

Sponsor: Universitätsklinikum Regensburg der Universität Regensburg

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Date: XX/Nov/2018

Signed ……
[Prof. Dr. P. Hau]

Note: This Development Safety Update Report contains confidential information. This report includes blinded adverse event data only.

EXECUTIVE SUMMARY

This fourth development safety update report (DSUR) for the NOA-07 trial (2007-002560-10) was prepared according to the ICH guideline E2F on development safety update report EMA/CHMP/ICH/309348/2008

This DSUR includes safety information from 13/Oct/2017-12/Oct/2018. The last chemotherapy cycle was applied from July until September 2015.

Characteristics of study treatment

The NOA-07 trial investigates the safety and efficacy of a standard therapy (radiotherapy) with the combination chemotherapy of cisplatin, lomustine and vincristine in adult patients with medulloblastoma.

Cisplatin is an alkylating chemotherapeutic agent. Mechanism of action is DNA crosslinking and inhibition of DNA repair. It is approved for treatment of various cancers and administered intravenously as an infusion.

In the NOA-07 trial, it was applied as a 6-hour infusion with a dose of 70 mg/m^2 every 6 weeks (day 1 and day 42).

Lomustine (CCNU) is one of the nitrosoureas. Its mechanism of action involves the inhibition of both DNA and RNA synthesis through DNA alkylation. It is cell cycle nonspecific and administered with orale capsules.

In the NOA-07 trial, oral capsules with a dose of 75 mg/m^2 every 6 weeks (day 1 and day 42) were administered.

Vincristine (Vincristine sulfate) is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant (*Vinca rosea).* The mechanism of action of Vincristine sulfate is the inhibition of microtubule formation in mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage. Vincristine was given concomitant during radiotherapy with weekly doses of 1,5 mg/m^2 (max. 2 mg) and during each adjuvant chemotherapy cycle at days 1, 8 and 15.

In total, chemotherapy consisted of vincristine during radiotherapy with weekly doses of 1, 5 mg/m^2 (max. 2 mg). Adjuvant chemotherapy consisted of maximum 8 six weekly cycles of cisplatin 70 mg/m^2, day 1; lomustine 75 mg/m^2, day 1; vincristin 1,5 mg/m^2 (max. 2 mg/m^2) day 1, 8 and 15. In cases of severe ototoxicity cisplatin could be replaced by carboplatin (400 mg/m^2). Dose reductions were prespecified in the study protocol depending on CTC criteria.

Exposure within the study

Within the study, 30 patients received study treatment. Vincristine was given with weekly doses during radiotherapy. Median number of applied doses per patient was 6.

Adjuvant chemotherapy consisted of maximum 8 six-weekly cycles of cisplatin, lomustine and vincristine. Maximum treatment duration was one year with 8 six-weekly treatment cycles. Median number of administered adjuvant chemotherapy cycles per patient was 6, median time on treatment approx. 9 months. Treatment of first patient was started on 26/Jan/2009, last chemotherapy cycle was administered on 27/Jul/2015. 3 patients are lost to follow up, 8 patients withdrew consent for further follow up and 5 patients died. All remaining patients have now finished a 3 year follow up period.

Approval status

Cisplatin, lomustine and vincristin are worldwide among the most widely used drugs in oncology and are approved and marketed worldwide.

Cisplatin and vincristine are among the 38 cytotoxcic substances of the WHO list of essential medicines (19th edition April 2015) that should be available for antineoplastic treatment in every country. Their individual safety profile is known for decades.

Safety assessment

From clinical trial information, literature research and our safety data, there no relevant new information on important known safety issues, most importantly hematologic toxicity and peripheral neurotoxicity, which appear to be the most frequent side effects of the combination chemotherapy in this dose. There are no SAR/SUSARs reported during the period of the study and literature review did not retrieve relevant new safety findings.

Since no safety concerns were newly identified nor significant new information relative to previously identified safety concerns was provided, the benefit-risk evaluation does not need to be re-considered.

Important risks

Hematotoxicity

Considering our safety data and the reviewed literature, hematologic toxicity (i.e. leukocytopenia and thrombopenia) is the leading toxicity of the combination treatment. 9/30 patients (30 %) experienced SARs due to hematologic toxicity of cisplatin and lomustine. In 7 patients (23%) the study treatment was terminated early due to hematologic toxicity, 3 of these 7 patients dropped out earlier than the 4th cycle of adjuvant chemotherapy.

However with median 6 applied cycles of chemotherapy, toxicity was manageable which was desirable for success of the treatment. 3 further SARs (infections) are to be seen in the context of hematologic toxicity.

Neurotoxicity

Neuropathy is another major toxicity of the study treatment. 2/30 patients (7%) experienced SAR related to peripheral neuropathy mostly caused by vincristine.

Additionally, 2/30 patients (7%) experienced abdominal SAR that are related to autonomous neuropathy.

Vincristine is probably the substance with most relevant effects on Quality of Life among the used chemotherapeutic agents. In NOA-07, safety data on neurotoxicity are in the range of the expected historic data.

Nephrotoxicity

1 patient (3% of patients) experienced severe acute renal failure - a percentage that is comparatively low for a treatment involving cisplatin.

Ototoxicity

1 patient (3% of patients) experienced severe hearing loss on top of preexisting hearing difficulties - again a percentage that is comparatively low for a treatment involving cisplatin.

Overall, the risks are fully consistent with experience from previous trials of the drugs and are covered in respective product characteristics of the drugs. Within the reporting period no additional SAR has been reported

Safety measures

The compiled safety data did not lead to actions for safety reasons like change of the IB, change of the informed consent form or change of the pharmaceutical information.

Conclusion

The safety information obtained in this reporting period justifies continuation of the study without changes. However, due to the low number of patients remaining in the study the scientific committee of NOA 07 recommended closure of the study.

Content

1. Introduction

This is the fourth development safety update report (DSUR) for the NOA-07 trial (EudraCT No.: 2007-002560-10) It was prepared according to the ICH guideline E2F on development safety update reports EMA/CHMP/ICH/309348/2008.

Rationale of the study

Primary aim of the NOA-07 study was to evaluate the toxicity of adjuvant chemotherapy with cisplatin, lomustine and vincristine in adults > 18 years of age with medulloblastoma in a controlled prospective setting.

In children with medulloblastoma, the introduction of adjuvant chemotherapy with cisplatin, lomustine and vincristine led to a significant improvement of the overall survival to a 5-year OS rate of >80 % (Packer *et al.,* 1994), (Packer *et al.,* 1999).

In adults, less and heterogeneous data existed, showing survival times varying between 26%-83% with various regimes in retrospective series. The only available prospective observation concerning adjuvant chemotherapy with cisplatin, lomustine and vincristine derived from the HIT88/89/91 study: 46 adults (age 16-51 years, median 21 years) were treated within the protocol reaching overall a 5y-PFS of 63% (n=46) and a 5y-PFS of 71% in cases of M0-situation (n=18) - a result that appeared promising and required prospective randomised trials for further validation**.**

However, toxicity concerns were raised when dealing with intensive adjuvant chemotherapy. In children, up to 60% of patients require dose modification. In adults, very little was known about the toxicity of the combination therapy. It was not possible to simply transfer the results from children to adults due to differing age-dependent chemotherapy sensitivities.

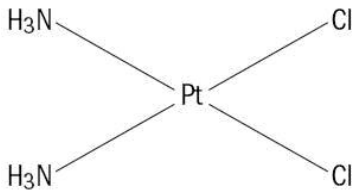
Accordingly, the scope of the NOA-07 trial was to accurately evaluate toxicity of an adjuvant treatment with cisplatin, lomustine, vincristine in a phase II study before planning a phase III trial on the efficacy on adjuvant chemotherapy in adult medulloblastoma.

Investigational drugs:

Cisplatin

Cisplatin is an alkylating chemotherapeutic agent. It was first used in 1974 for treatment of testicular cancer. It is administered intravenously as an infusion. Mechanism of action is DNA crosslinking, inhibition of DNA repair and ultimately apoptosis of dividing cells.
In the NOA-07 trial, it was applied as a 6-hour infusion with a dose of 70 mg/m^2 every 6 weeks (day 1 and day 42). In cases of severe ototoxicity it was to be replaced by Carboplatin (400 mg/m^2).

The structural formula is:

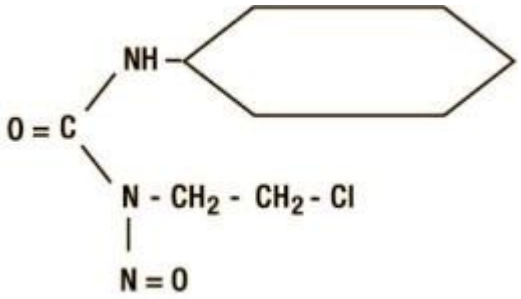


$PtCl_2H_6N_2$ M.W. 300.04

Lomustine

Lomustine (CCNU) is one of the nitrosoureas. It is 1-(2-chloro-ethyl)-3-cyclohexyl-1-nitrosourea. It is a yellow powder with the empirical formula of $C_9H_{16}ClN_3O_2$ and a molecular weight of 233.71. It is taken as an oral capsule.

The structural formula is:



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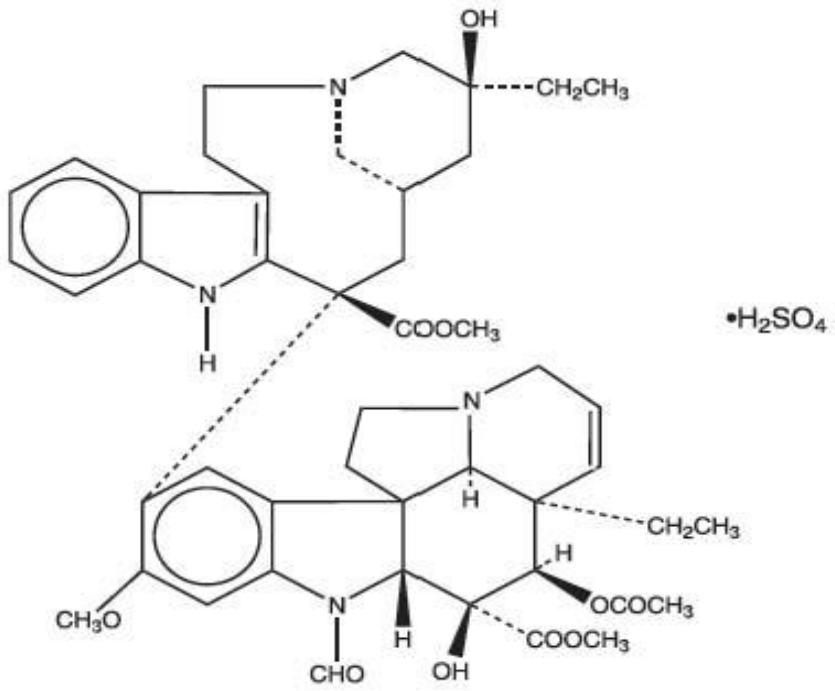
Its mechanism of action involves the inhibition of both DNA and RNA synthesis through DNA alkylation. Lomustine has been shown to affect a number of cellular processes including RNA- and protein synthesis, and the processing of ribosomal and nucleoplasmic messenger RNA, DNA base component structure, the rate of DNA synthesis and DNA polymerase activity. It is cell cycle nonspecific.

In the NOA-07 trial oral capsules with a dose of 75 mg/m^2 every 6 weeks (day 1 and day 42) were administered.

Vincristine

Vincristine Sulfate is the salt of an alkaloid obtained from a common flowering herb, the periwinkle plant (*Vinca rosea* Linn). Originally known as leurocristine, it has also been referred to as LCR and VCR. The molecular formula for Vincristine Sulfate, USP is $C_{46}H_{56}N_4O_{10}•H_2SO_4$. It has a molecular weight of 923.04.

The structural formula is:



The mechanism of action of Vincristine sulfate is the inhibition of microtubule formation in the mitotic spindle, resulting in an arrest of dividing cells at the metaphase stage.

Vincristine was given concomitant during radiotherapy with weekly doses of 1,5 mg/m^2 (max. 2 mg) and during each adjuvant chemotherapy cycle at days 1, 8 and 15.

A study overview of the NOA-07 trial is given underneath:

Re-section	**Radio-therapy**	**Adjuvant Chemotherapy with cisplatin, lomustine and vincristine: 8 cycles, every six weeks**
	VCR (weekly)	

<---------- Treatment duration 1 year ---------->

Chemotherapy

Adjuvant chemotherapy consisted of maximum 8 six weekly cycles of cisplatin 70 mg/m^2, day 1; lomustine 75 mg/m^2, day 1, vincristine 1,5 mg/m^2 (max. 2 mg/m^2) day 1, 8 and 15.

During the study all study drugs were prepared locally by the pharmacies of the participating centres.

Radiotherapy

Radiation of brain and neuraxis consisted of 22x1,6 Gy (5/week) to a total dose of 35,2 Gy, followed by a posterior fossa boost of 11x1,8 Gy (5/week) to 55 Gy.

In cases of metastatic disease an additional boost to cereberal metastases 11x 1.8 Gy (5/week) or spinal metastases 8x1,8 Gy (5/week) was applied.

Please see the Investigator's Brochure submitted in appendix 1 for further details.

2. Worldwide Marketing Authorization Status

Cisplatin, lomustine and vincristine are worldwide among the most widely used drugs in oncology. Cisplatin and vincristine belong to the 38 cytotoxcic substances of the WHO list of essential medicines (19th edition April 2015) i.e. they should be available for antineoplastic treatment in every country.

Cisplatin was first approved in the US by the FDA on 19/Dec/1978. In Germany, it was approved on 06/Sep/1983. The use of cisplatin is approved for testicular, ovarian, bladder, head and neck, esophageal, small and non-small cell lung, cervical, stomach, uterus cancers and for treatment of sarcoma. Approved doses vary between 20 mg/m^2 per day for 5 days, every three/four weeks, single doses up to 100 mg/m^2 every three/four weeks or 40 mg/m^2 weekly for up to six weeks.

Vincristine was first approved in the US by the FDA on 10/Jul/1968. Approval in Germany

occurred shortly later. It is approved in combination therapies for acute leukemia, Hodgkin's and non- Hodgkin's lymphoma, neuroblastoma, neuroblastoma, rhabdomyosarcoma, osteosarcoma, Ewing's sarcoma, Wilms' tumor, metastasized breast cancer, small cell lung cancer, glioma and in monotherapy for idiopathic thrombocytopenic purpura. The approved dose of vincristine is 1,4-1,5 mg/m^2 intravenously given once weekly, maximum dose per week is 2 mg.

Lomustine was first approved in the US by the FDA on 04/Aug/1976. In Germany, it was approved on 26/Nov/1980. It is approved for combination therapies for treatment of malignant glioma, Hodgkins disease, small cell lung cancer, malignant melanoma and brain metastases of other tumors. Approved doses in mono- or combination therapy vary between 70-110 mg/m^2 every 6-8 weeks. A cumulative dose of 1000 mg/m^2 should not be exceeded due to the danger of lung fibrosis.

3. Actions Taken in the Reporting Period for Safety Reasons

The compiled safety data did not lead to actions for safety reasons like change of the study protocol, change of the informed consent form or any other actions.

4. Changes to Reference Safety Information

The safety section of the study protocol has not been changed during the reporting period.

5. Inventory of Clinical Trials Ongoing and Completed by the sponsor during the Reporting Period

Table 1

Study ID	EUDRACT 2007 – 002560 – 10
Phase	II
Status	Ongoing, recruitment and treatment finished
Country	Germany
Study Title	Multicentre pilot study for the treatment of medulloblastoma in adults – the NOA-07 trial
Study design	Single arm
Dosing regimen	Vincristine was given during radiotherapy with weekly doses of 1,5 mg/m^2 (max. 2 mg). Adjuvant chemotherapy consisted of maximum 8 six weekly cycles of cisplatin 70 mg/m^2, day 1; lomustine 75 mg/m^2, day 1; vincristin 1,5 mg/m^2 (max. 2 mg/m^2) day 1, 8 and 15.
Study population	30 patients, male and female with medulloblastoma, age>18 years
FVFP	26/Jan/2009
Planned enrolment	30
Subject exposure	30

Detailed description:

This DSUR covers a single study: "Multicenter Pilot-study for the Therapy of Medulloblastoma of Adults (NOA-07)". Other studies of the sponsor with the involved treatments are not ongoing or completed.

The primary objectives of this pilot study are to assess the incidence of therapy related treatment terminations, to determine the toxicity (especially myelo-, neuro-, oto- and nephrotoxicity) of adjuvant chemotherapy and to determine the number of feasible chemotherapy cycles in adults. Secondary objective of the study is the determination of the 3-year and 5-year PFS rate in adult patients. Apart from this, quality of life, neurocognitive

deficits, endocrinologic parameters, fertility and leucencephalopathy will be determined during the study. The influence of factors at diagnosis (metastasis, histology, hydrocephalus, tumor size) on the prognosis of the disease will be determined.

The NOA-07 study (EUDRACT 2007 – 002560 – 10) is a single arm, phase II study. From January 2009 to April014, it recruited 30 adult patients in 15 German centers (male and female, age >18 years). The study was approved by the BfArM on 13th/Oct/2008.

Investigational medicinal product (IMP) consisted of the combination of vincristine during radiotherapy with weekly doses of 1,5 mg/m^2 (max. 2 mg per week) i.v. and maximum of 8 cycles adjuvant chemotherapy after radiotherapy. Each adjuvant chemotherapy cycle comprised vincristine with 1,5 mg/m^2 (max. 2 mg per week) i.v. at day 1,8 and 15; cisplatin 70 mg/m^2 (i.v. for 6-hours), day 1; lomustine 75 mg/m^2 (orally), day 1 of each cycle. It was repeated after 6 weeks at day 42. The first cycle was given 6 weeks after end of radiotherapy.

An independent DMC decided regularly about the course of the study, The trial would have been terminated prematurely if at least 10 patients had unexpectedly cancelled adjuvant chemotherapy prior to the 4th cycle.

According to grades of toxicity (myelo-, oto-, neuro-, nephrotoxicity and weight loss), a dose adaption scheme (see appendix 1, study protocol page 32-33) was provided by the sponsor.

Treatment of first patient was started on 26/Jan/2009, and recruitment was stopped in April 2014 after recruitment of the last patient. Last adjuvant chemotherapy cycle was started on 27/Jul/2015.

The primary study endpoint was the number of therapy related treatment terminations, which comprised:

- any toxicity grade IV according to the CTC score V3.0 (modification of ARO/AIO and ADT) before or at the same time as the treatment termination
- termination of treatment with an explanation of a toxicity < CTC Grade IV

- patient death irrespective of cause of death.

Documentation forms of chemotherapy cycles needed to be sent to the sponsor at maximum 4 weeks after completion of each cycle.

3 patients are lost to follow up, 8 patients withdrew consent for further follow up and 5 patients died. All remaining patients have now finished a 3 year follow up period. The study was closed in October 2018.

Please see the study protocol (appendix 1) for further details on course of the study

6. Estimated Cumulative Exposure

6.1 Cumulative Subject Exposure in the Development Program

This DSUR is based on safety data of a single clinical trial, there is only information about cumulative numbers of exposed subjects within this study.

33 patients were included in the study (21 male, 12 female patients), 2 patients were excluded by the sponsor as they were not treated in registered study centres, one patient withdrew informed consent before beginning of treatment, 30 patients were treated within the study with the IMP (19 male and 11 female patients). One patient withdrew consent later in the study.
Median patient age was 36 years (range 21-53 years).

Table 2

Subject exposure to IMP by age and gender

		Age range 18-35 yrs.		Age range 35-51 yrs.		Racial group
Treatment	**# of subjects**	**m**	**f**	**m**	**f**	**Caucasian**
Cisplatin/ Vincristine/ Lomustine	30	7	6	12	5	N.A.

Last adjuvant chemotherapy cycle was applied at 27/Jul/2015, no further acute toxicity is expected.

Vincristine was given with weekly doses during radiotherapy. Median number of applied doses per patient was 6.
Adjuvant chemotherapy consisted of maximum 8 six-weekly cycles of cisplatin, lomustine and vincristine. Median number of administered cycles per patient was 6.

All patients were recruited in Germany. Data on racial background was not compiled within the study.

As treatment is stopped no additional patients will receive chemotherapy within the NOA-07 trial.

No further data on cumulative subject exposure is available. The trial drug is a marketed drug and the sponsor doesn't have access to further data.

6.2 Patient Exposure from Marketing Experience

Cisplatin, lomustine and vincristine are not marketed by the sponsor.

At present and in recent future few patients in Germany receive chemotherapy according to the NOA-07 trial.

7. Data in Line Listings and Summary Tabulations

7.1 Reference Information

As an investigator initiated trial, we used the CTC (Common Toxicity Criteria) Grading Version 3.0 modified according to ARO / AIO und ADT for the grading of adverse events and for assessment of SOCs ().

The actual summaries of product characteristics (see appendix 2) served as the reference document for determination of "expectedness" for all adverse events. Relevant safety data are presented using interval line listings and cumulative summary tabulations.

7.2 Line Listings of Serious Adverse Reactions (SARs) during the Reporting Period

No SAR during reporting period.

7.3 Cumulative Summary Tabulations of Serious Adverse Events

see Appendix 3

8. Significant Findings from Clinical Trials during the Reporting Period

8.1 Completed Clinical Trials

Not applicable. NOA-07 (2007 – 002560 – 10) is the only trial which is conducted by the sponsor with this IMP and the only study covered by this DSUR, and it is ongoing.

8.2 Ongoing Clinical Trials

NOA-07 (2007 – 002560 – 10) is the only trial covered by this DSUR. It is ongoing.

Regarding efficacy, there have been no results from NOA-07 (2007 – 002560 – 10) generated yet.

There have been no SARs or other significant findings during the reporting period. For further details see chapters 16 and 18.

8.3 Long-Term Follow-up

0 patients are in follow up longer than 5 years after end of study.

8.4 Other Therapeutic Use of Investigational Drug

Not applicable. The sponsor does not conduct any expanded access or compassionate use programmes for cisplatin/vincristine/lomustine.

8.5 New Safety Data Related to Combination Therapies

Not applicable, no data available.

In the period covered, the study treatment was not combined with other chemotherapeutic agents in prospective trials.

9. Safety Findings from Non-interventional Studies

No data concerning safety findings from observational or epidemiological studies are available to the sponsor.

10. Other Clinical Trial/Study Safety Information

Not applicable.

11. Safety Findings from Marketing Experience

All substances are not being marketed by the sponsor. To our knowledge, there have been no "Rote Handbriefe" or other reports on severe safety issues of the study drugs in the period covered. No other data concerning safety findings from marketing experience or off-label use are available to the sponsor.

12. Non-clinical Data

Non-clinical data are summarized in the last available versions of summary of product characteristics of cisplatin/vincristine/lomustine (see Appendix 2).

All parts of the combination treatment have a negative impact on reproductive potential and are known to be potentially carcinogenic and embryotoxic.

13. Literature

Analysis of efficacy of combined radio-chemotherapy in medulloblastoma

Two reports from different groups (Hadi et al. 2017, Atalar et al. 2018) examined the effect of radio- and radiochemotherapy in adult medulloblastoma. Both reports showed benefical prognostic effects of combined radiochemotherapy .

Monotherapy with either lomustine or vincristine or cisplatin

At clinical trial.gov no study results on monotherapy of the individual components have been published in the period covered.

We performed a Pubmed inquiry covering the reporting period with the items: " lomustine and medulloblastoma", "cisplatin and medulloblastoma", "vincristine and medulloblastoma"

Lomustine

Unexpected safety data that is not included in the pharmaceutical information was not encountered in Pubmed.

Vincristine

One report outlined a prospective monocentric experience with application of glutamine for prevention of neurotoxic effects of vincristine. This publication showed a signal for efficacy (Sands et al. 2017). A multicentric approach is warranted.

Unexpected safety data that is not included in the pharmaceutical information was not encountered in Pubmed.

Cisplatin

Two publications describe the relevance of cisplatinum dose (< 400 mg/m2) and of radiation dose in the cochlea (< 45 Gy) for prevention of ototoxicity (Scobioala et al 2017, Waissbluth et al. 2018).

Unexpected safety data that is not included in the pharmaceutical information was not encountered in Pubmed.

Publications that would change the further course of the trial were not encountered.

14. Other DSURs

No further DSURs for this IMP are currently issued by the sponsor. No DSURs were provided by other sponsors conducting clinical trials with the same investigational drugs during the reporting period.

15. Lack of efficacy

There is no indication of lack of efficacy.

16. Region-Specific Information

16.1 Cumulative Summary Tabulation of Serious Adverse Reactions

At 23/Oct/2017 a total of 27 SARs have been reported to the Sponsor. None of them occurred during the reporting period. A cumulative summary tabulation of SARs is presented in Appendix 4.

16.2 List of Subjects Who Died during the Reporting Period

No patient died during the reporting period.

16.3 Subjects who Dropped Out in Association with any Adverse Event in the Reporting period

No patients dropped out during the reporting period in due to any adverse event

16.4 Significant Phase I Protocol Modifications
None

16.5 Significant Manufacturing Changes
Not applicable.

16.6 Description of the General Investigation Plan for the Coming Year
Not applicable.

16.7 Log of Outstanding Business with Respect to the US IND
Not applicable

17. Late-Breaking Information
None

18. Overall Safety Assessment

From clinical trial information, literature research and our safety data, there is no relevant new information on safety issues, most importantly hematologic toxicity and peripheral neurotoxicity, which appear to be the most frequent side effects of the combination chemotherapy in this dose. There are no SAR/SUSARs reported during the period of the study and literature review did not retrieve new safety findings.

Since no safety concerns were newly identified nor significant new information relative to previously identified safety concerns was provided, the benefit-risk evaluation does not need to be re-considered.

18.1 Evaluation of the Risks
Overall, the combination treatment was tolerated without excessive toxicity. Among the

known safety concerns particularly hematologic toxicity, infections (related to hematologic toxicity), peripheral neurotoxicity and gastrointestinal toxicity (related to neurotoxicity) have been observed in the study. In the reporting period no additional SAR occurred.

18.2 Benefit-risk Considerations

At the present stage of development, the risk of postoperative radiotherapy in combination with the chemotherapy of cisplatin, vincristine and lomustine appears acceptable in light of its potential significant improval of PFS and OS. Since no safety concerns were newly identified, nor significant new information relative to previously identified safety concerns was provided, the benefit-risk evaluation does not need to be re-considered.

19. Summary of Important Risks

19.1 Hematologic toxicity

Considering our safety data and the reviewed literature, hematotoxicity (i.e. leukocytopenia and thrombopenia) is the leading toxicity of the combination treatment. 9/30 patients (30%) experienced SARs due to hematologic toxicity. Cisplatin and - in particular - lomustine in the adjuvant part of chemotherapy are here causative. In 7 patients (23%) the study treatment was terminated early due to hematotoxicity,

However, with the applied close blood count monitoring and predefined dose reductions the toxicity was manageable and most patients could reach more than 4 cycles of adjuvant chemotherapy which is desirable for success of the treatment (median applied doses: 6 cycles). 3 patients dropped out earlier than the 4th cycle of adjuvant chemotherapy. 3 further SARs (infections) are to be seen in the context of hematologic toxicity.

19.2 Neurotoxicity

Considering our safety data and the reviewed literature, neurotoxicity, i.e. peripheral neuropathy and autonomous neuropathy with gastrointestinal symptoms (pain, constipation, paralytic ileus), is another major toxicity of the study treatment.

4/30 patients (13%) experienced SARs related to peripheral neuropathy or autonomous neuropathy with gastrointestinal symptoms mostly caused by vincristine. We expect that

after full analysis of data (including electrophysiologic tests), some more patients will show signs of mild or moderate neuropathy. Vincristine is probably the substance with most relevant effects on QoL among the used chemotherapeutic agents. If primary dose reductions or omitting of the substance is feasible in treatment of medulloblastoma should be evaluated in future studies. For the moment this safety data is in the range of the expected historic data.

19.3 Nephrotoxicity

1 patient (3% of patients) experienced severe acute renal failure - a percentage that is comparatively low. We think that this reflects safety measures that have been taken before inclusion of patients and adequate hydration before/during infusion.

19.4 Ototoxicity

1 patient (3% of patients) experienced severe hearing loss on top of preexisting hearing difficulties – again a percentage that that is comparatively low. We expect that after full analysis of data including audiograms, a higher percentage of patients will show measurable hearing loss, hopefully without subjective hearing loss and without loss of QoL.

20. Conclusions

The risks are fully consistent with experience from previous trials of the drugs and are covered in the respective product characteristics of the drugs.

We conclude that the information obtained in this reporting period justifies continuation of the study without change.

21. References

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Waissbluth S, Del Valle Á, Chuang A, Becker A. Incidence and associated risk factors for platinum-induced ototoxicity in pediatric patients.Int J Pediatr Otorhinolaryngol. 2018 Aug;111:174-179. Doi: 10.1016/j.ijporl.2018.06.021. Epub 2018 Jun 12.

Appendices to the DSUR

1 Study protocol

2 Actual summaries of pharmaceutical product characteristics (cisplatin, vincristine, lomustine)

3 Cumulative Summary Tabulation of Serious Adverse Events (SAEs):

4 Line Listings of Serious Adverse Reactions (SARs)