

[ICH E2F]

[EXAMPLE DSUR – PHASE III INVESTIGATIONAL DRUG]

ZB3579

Development Safety Update Report #4

Period covered: 1st January 2009 – 31st December 2009

Note: This report contains unblinded clinical trial adverse event data

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EXECUTIVE SUMMARY

- This is the 4th annual DSUR for ZB3579, summarising safety data received by Zoboryn Pharmaceuticals from 1st January - 31st December 2009.
- ZB3579 is an alpha-6-acetylhydrotransferase inhibitor being developed for the treatment of gastro-oesophageal reflux disease (GERD), given orally as 10-20 mg tablets once daily.
- Overall, approximately 3800 patients and healthy volunteers have been enrolled into the ZB3579 clinical development programme; approximately 2900 subjects have received ZB3579. ZB3579 is not authorised for sale in any country at the time of this report.
- Following a review of data from recently completed Phase II dose-ranging trials, the following are identified as possible adverse reactions associated with ZB3579: headache, nausea, abdominal pain, flatulence, diarrhoea and skin rash. These were usually mild in nature. Most of the events resolved despite continued therapy, although skin rash required cessation of therapy to achieve resolution in many instances. The Investigator's Brochure has been updated accordingly.
- A recently completed 12-month dog study indicated an association with mild dose-related hepatic inflammatory changes. Although there was limited evidence of adverse liver effects in Phase I/II trials, Phase III trial protocols have been amended to manage any potential risk of liver injury to trial subjects, with additional exclusion criteria, enhanced liver function test (LFT) monitoring and stopping rules. In addition, a Data Monitoring Committee has been established to provide real-time oversight of the ongoing safety data.
- Three cases of pancreatitis have now been reported during the clinical development programme. A causal relationship with ZB3579 has not been determined as there are plausible alternative explanations for each case.
- The following have been identified as important potential risks, to be closely monitored as the Phase III clinical programme progresses: liver toxicity, pancreatitis, severe skin reactions.

- Taking into account the measures taken to minimise risk to patients participating in the Phase III clinical trials, the potential risks identified in association with ZB3579 are justified by the anticipated benefits that may be afforded to patients with GERD.

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1 Introduction

This is the 4th DSUR prepared by Zoboryn Pharmaceuticals as the worldwide sponsor of the ongoing clinical development programme for ZB3579; the Development International Birth Date is 16th January 2006. This DSUR summarises safety data arising from the world-wide ZB3579 clinical development programme and received by Zoboryn between 1st January 2009 and 31st December 2009, and is compiled in accordance with the ICH E2F (DSUR) guideline.

ZB3579 is a potent and highly selective inhibitor of alpha-6-acetylhydrotransferase, an intracellular enzyme involved in the production of gastric acid. In clinical pharmacology studies, ZB3579 10-40 mg tablets once daily suppressed gastric acid levels completely in all healthy volunteers tested. Reducing gastric acid levels has been shown to have a beneficial effect in a variety of disorders, including gastro-oesophageal reflux disease (GERD), gastritis and peptic ulceration.

ZB3579 is currently being investigated for the treatment of adults with GERD as its primary indication. It is anticipated that it will differ from established therapies (proton pump inhibitors and H₂-antagonists) with more rapid, complete and longer-lasting suppression of gastric acid, thereby improving the effectiveness of the treatment of GERD.

Zoboryn is the sole sponsor of ZB3579 clinical trials. ZB3579 has not been supplied for investigator-sponsored trials, nor for compassionate or named-patient use.

2 Worldwide Marketing Approval Status

ZB3579 is not authorised for sale in any country at the time of this report.

3 Actions Taken in the Reporting Period for Safety Reasons

In light of evidence of inflammation of the liver in 12-month dog studies (see Section 12.2; Non-clinical data - liver findings), it has been agreed with the relevant regulatory authorities and ethics committees that the protocols for ongoing Phase III studies should be amended to include additional exclusion criteria, stopping rules and enhanced monitoring of liver function tests (LFTs). In addition, the ZB3579 Investigator's Brochure has been updated, patients have signed revised informed consent forms in order to continue in the studies, and a Data Monitoring Committee has been established to review safety data from the programme on an ongoing basis (see Section 18.1.3; Evaluation of the risks - liver findings).

A cumulative table of important regulatory requests regarding the ZB3579 development programme is provided in Appendix 2. Earlier preclinical investigations demonstrated that ZB3579 blocks hERG-encoded potassium channels with an IC₅₀ value of 0.09 µM, which is approximately 10-fold higher than the C_{max} observed in humans following administration of ZB3579 40 mg once daily. A ‘Thorough QT study’ was completed in October 2007, before initiation of the Phase II clinical trials. The results indicated that a single 400mg dose of ZB3579 had no effect on ventricular repolarisation during the first 24 hours after administration, with no individual exhibiting QTcF >500 msec and with no change from baseline in QTcF > 20 msec. All other intervals were within the physiologic range. However, one study subject experienced a 3 second sinus pause within 1 hour of dosing with 400mg ZB3579. As a result of this finding, US FDA requested that all study subjects should undergo Holter monitoring during the US Phase II clinical trial (3579DD/014) - the results of this monitoring are summarised in Section 8.1.

4 Changes to Reference Safety Information

The Investigator’s Brochure (IB) provides a summary of clinical and non-clinical data for the product relevant to its study in human subjects. Section 7 of the ZB3579 IB (Summary of Data and Guidance for the Investigator) provides investigators with a clear understanding of the possible risks, adverse reactions, specific tests, observations and precautions relevant to ZB3579, and acts as the reference safety information for the purposes of this report.

Following a review of the data arising from the completed Phase II studies, it was decided that the following should be added as adverse reactions to Section 7 of the ZB3579 IB in August 2009: nausea, abdominal pain, flatulence, diarrhoea and skin rash. The Phase II data indicate that headache and the gastrointestinal effects were usually mild in nature and resolved even when therapy was continued. However, although skin rash was usually mild and maculopapular in nature, cessation of therapy was often required for resolution to occur.

The IB was updated in December 2009 to provide details of liver findings from 12-month dog studies and the measures being taken to minimise potential risk to study subjects in ongoing clinical trials (see Sections 12.2 and 18.1.3 for further details). As the latest version has not yet been submitted to relevant regulatory authorities, a copy is provided with this DSUR (Appendix 1).

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

Two Phase II dose-response studies were completed during the reporting period. Patients with GERD were treated for up to 6 weeks with 5, 10, 20 or 40 mg ZB3579 (n=1665) or 40 mg esomeprazole (n=409) once daily. The results indicated that ZB3579 suppressed gastric acid effectively in patients with GERD, leading to improvement in endoscopic findings and symptoms, and supported a decision to enter into Phase III development. It was decided that the Phase III programme should evaluate 10-20 mg ZB3579 once daily, as the Phase II studies indicated that the 5 mg dose was only partially effective, while the 40 mg dose had limited additional effectiveness over the 20 mg dose with a greater proportion of adverse reactions seen at the higher dose.

The first Phase III clinical trial was initiated on 2nd August 2009. By 31st December 2009, 1011 patients had been enrolled into three clinical trials comparing the effectiveness of ZB3579 (10 mg once daily and 20 mg once daily for up to 12 weeks) in the treatment of GERD with esomeprazole or lansoprazole, with two-thirds of patients receiving ZB3579 according to the randomisation schemes. In addition, two studies were initiated during the reporting period to investigate patients with renal and hepatic impairment and a third study initiated to compare the bioavailability of the Phase II and III formulations.

Further details for each clinical trial completed and ongoing during the reporting period are provided in Appendix 3.

6 Estimated Cumulative Exposure

6.1 Cumulative Subject Exposure in the Development Programme

Overall, 388 healthy volunteers and over 3400 patients have been enrolled into the ZB3579 clinical programme, of which approximately 2900 subjects have received ZB3579. In total, 2074 patients participated in the Phase II programme, and over 1000 patients have enrolled into the Phase III studies.

Healthy volunteers have received ZB3579 as single doses or as multiple doses for up to 7 days. Patients with GERD have received ZB3579 5-40 mg daily from 14 days to 12 weeks during the clinical development programme.

Estimates of overall cumulative subject exposure are provided in Table 1, based upon actual exposure data from completed studies and the enrollment/randomization schemes for ongoing studies.

Table 1 Estimated Subject Exposure in ZB3579 Clinical Studies*

Treatment	Number of subjects**
ZB3579	2938
Esomeprazole/lansoprazole	782
Placebo	201
Other comparators	106

* includes patients and healthy volunteers, as of 31st December 2009

** includes subjects that have received ZB3579 and comparators during crossover studies

An estimate of cumulative exposure to ZB3579 by age, sex and racial group is provided in Appendix 4.

There has been limited experience among females of childbearing potential, in line with the exclusion criteria for the Phase I-II clinical studies. Reproductive toxicity studies have been completed, demonstrating no adverse effects on fertility or foetal development in rats or rabbits. Hence, females of childbearing potential are now allowed into the Phase III studies providing that they utilise effective means of contraception – this will provide significant experience in this patient group.

6.2 Patient Exposure from Marketing Experience

ZB3579 is not authorised for sale in any country at the time of this report.

7 Data in Line Listings and Summary Tabulations

Relevant safety data are presented using interval line listings (serious adverse reactions) and cumulative summary tabulations (serious adverse events) in Appendices 5 and 6 respectively.

7.1 Reference Information

The Medical Dictionary for Regulatory Activities (MedDRA) version 12.1 has been used for the coding of adverse events. The line listings and the summary tabulations are arranged alphabetically by primary System Organ Class (SOC) and Preferred Term (PT) level.

For the purpose of this report, an unexpected adverse reaction is one that is not consistent with the ZB3579 reference safety information at the start of the DSUR period, noting that the ZB3579 IB was amended in June 2009 to include the following as adverse reactions: nausea, abdominal pain, flatulence, diarrhoea and skin rash.

7.2 Line Listings of Serious Adverse Reactions during the Reporting Period

During the reporting period, 94 serious adverse events (SAEs) were reported in 82 patients, of which 27 SAEs were considered as being possibly related to study drug by the reporting investigators and/or Zoboryn. Details of these 27 serious adverse reactions are provided in Appendix 5. Each case report appears only once within the line listing, and is presented in the primary SOC determined by the most serious adverse reaction for the case, as judged by Zoboryn.

The drug identity is provided for all case reports that include unblinded data. For case reports where the code break has yet to be completed, the drug is identified as 'Blinded'.

7.3 Cumulative Summary Tabulations of Serious Adverse Events

Appendix 6 presents a cumulative table of the number of serious adverse events (SAEs) that have been reported during the ZB3579 clinical development programme, from its initiation to the data lock point (31st December 2009), organized by SOC. Appendix R1 presents an analogous table of the number of serious adverse reactions (i.e., as 'possibly related SAEs'); asterisks identify 'unexpected' terms assigned at the MedDRA PT level within this table.

Both tables present SAE counts under the following column headings: Study Drug (ZB3579), Placebo, Comparator and 'Blinded'. Where two SAEs for the same trial subject code to the same MedDRA PT, they have been counted as one event at the PT level in the tabulation.

8 Significant Findings from Clinical Trials during the Reporting Period

8.1 Completed Clinical Trials

During the reporting period, Zoboryn analysed data from two completed dose-response clinical trials (3579DD/0013 and 3579DD/0014) investigating ZB3579 in the treatment of GERD when given for 6 weeks. The data indicate that ZB3579 (10-40 mg once daily) is effective in rapidly suppressing gastric acid levels, with symptomatic relief and improvement in endoscopic findings, sufficient to support a decision to initiate a Phase III clinical trial programme with esomeprazole and lansoprazole as active comparators.

A healthy volunteer experienced a 3-second sinus pause during the 'Thorough QT study' (see Section 3), thus investigators in study 3579DD/0014 conducted Holter monitoring in all trial participants during the first week after initiation of therapy with ZB3579 (or comparators). There were no additional reports of sinus pause or symptomatic bradyarrhythmias. There were no differences among the treatment groups for the occurrence of supraventricular or ventricular arrhythmias, such that it was considered that Holter monitoring was unnecessary during the Phase III trials.

Two cases of pancreatitis were reported during the Phase II clinical trial programme during early 2009. The first report concerned a 52 year old female with a medical history including GERD, back pain, hiatus hernia, hyperlipidaemia, type 2 diabetes and chronic obstructive pulmonary disease (3579DD/013/002/023). Her concurrent medications included metformin and simvastatin. She was hospitalised with acute epigastric pain, nausea and vomiting, diagnosed as acute pancreatitis with moderately elevated lipase and amylase values (up to 226 U/L and 184 U/L respectively). It was noted that the patient had been consuming alcohol at several parties during the previous week. At the time of admission, the patient had been taking ZB3579 20 mg once daily for 8 weeks; the study drug was discontinued at the time of hospitalisation. The investigator considered the adverse event to be possibly related to study drug or simvastatin, and the patient was withdrawn from the study. The patient has since fully recovered.

The second report (3579DD/013/011/008) related to a 46 year old female with a history of GERD and primary sclerosing cholangitis who was admitted with worsening abdominal pain, diagnosed as acute pancreatitis with elevated lipase and amylase values (up to 489 IU/L and 733 U/L respectively). Study drug was discontinued upon admission to hospital and the patient withdrawn from the trial – the patient received ZB3579 40 mg once daily for 23 days

prior to hospital admission. The patient recovered from this event, and the investigator considered the event as unrelated to study drug.

In addition, noting that skin rash has been identified as a possible adverse reaction associated with ZB3579, a case report of erythema multiforme was reported during February 2009. This concerned a 67-year-old male with a medical history of GERD and coronary artery disease who developed pruritic papular erythema on the neck, buttock areas, upper limbs, and back after treatment with ZB3579 10 mg once daily for 5 weeks (3579DD/014/007/014).

Concomitant medications included fluindione, fish oil capsules and atenolol. Although no specific diagnostic investigations were performed, erythema multiforme was diagnosed. The event resolved after withdrawal of ZB3579 and treatment with fexofenadine for 15 days.

8.2 Ongoing Clinical Trials

In addition to the two case reports of pancreatitis received in early 2009 (see Section 8.1), another case report of pancreatitis was received during December 2009. This concerned an obese 58 year old male with a history of heavy drinking, GERD, cirrhosis and previous pancreatitis (3579DD/016/003/004). The patient was hospitalised with abdominal pain, back pain, nausea and vomiting for the previous two days, diagnosed as acute pancreatitis with elevated lipase and amylase values (up to 436 IU/L and 689 U/L respectively). The patient had received study medication for 4 weeks prior to the onset of this event. Study medication was stopped and the patient made a full recovery following symptomatic treatment. The investigator considered the adverse event unrelated to study drug, and the treatment code remains unbroken, pending study completion.

In addition, there has been a case report of 'hepatitis' received following the data-lock point, which is currently subject to follow-up to obtain further clinical details (see Section 17; Late-Breaking Information).

8.3 Long-term Follow-Up

At present, patients completing ZB3579 studies are not subject to long-term follow up.

8.4 Other Therapeutic Use of Investigational Drug

No pre-approval patient access programmes have been initiated for ZB3579.

8.5 New Safety Data Related to Combination Therapies

This section is not applicable as ZB3579 is a monotherapy.

9 Safety Findings from Non-interventional Studies

No observational or epidemiological studies of ZB3579 have been initiated, conducted, completed or reported during the period under review.

10 Other Clinical Trial/Study Safety Information

No other studies have been conducted with ZB3579.

11 Safety Findings from Marketing Experience

ZB3579 is not approved for marketing in any country.

12 Non-Clinical Data

Data from recently completed 6-month rat and 12-month dog studies with ZB3579 have been analysed. Relevant findings are summarised below.

12.1 Gastric effects

The stomachs of all rats and dogs treated with ZB3579 had thickened mucosal surfaces and linked morphological changes related to the trophic effect of hypergastrinemia caused by a prolonged and pronounced inhibition of gastric acid secretion of the test compound. These changes are previously well-documented in 3-month rat and dog studies with ZB3579, and analogous studies of proton pump inhibitors, and are considered to be exaggerated pharmacological effects/adaptive changes resulting from the acid inhibition.

12.2 Liver findings

Clinical pathology measurements have demonstrated small but sustained increases in alanine aminotransferase (ALT) levels at all doses (1, 10 and 50 mg/kg/day) following 12-month oral administration of ZB3579 to dogs that was time and dose-dependent, with recovery during dose-free periods.

In addition, histopathological examination showed minor inflammatory changes in the liver. All of the dogs (including the control group) exhibited scattered foci of centrilobular inflammation within the liver, recorded as minimal in severity. However dogs from the intermediate and high dose groups also exhibited changes consistent with a chronic

inflammatory pattern. The severity of the inflammation was recorded as minimal or mild, and the incidence of centrilobular inflammation was greater in the high dose males in comparison to the control group. There was also increased amounts of connective tissue in the livers of treated animals, consistent with chronic inflammation, and the presence of lipofuscin in the pigmented macrophages, indicative of increased cell turnover.

The findings had a strong correlation with increased ALT levels observed in the treated dogs, such that the sustained elevations of ALT seem to be a reliable marker of liver injury preceding the development of the histopathological changes. ALT is essentially liver-specific in the dog and elevations generally indicate hepatocyte damage. The half-life of ALT in dogs is relatively short and as such the increased levels seen throughout the study are consistent with subtle low-grade hepatocellular damage.

In contrast, ALT elevations were not evident and no liver histopathological findings have been observed following 6-months administration in rats or 3-months administration in dogs.

The clinical implications of these findings are considered in Section 18.1.3 of this DSUR.

12.3 Irritability

In a previous 4-week toxicology study, ZB3579 was administered orally to male and female dogs at doses up to 50 mg/kg/day: irritability was observed in the groups administered 10 and 50 mg/kg/day. However, in the 12-month dog study, with ZB3579 administered orally to male and female dogs at similar doses, irritability was not observed in any group. The reason for this difference is unknown, noting that the studies were of different duration and conducted by different contract laboratories.

Irritability was not observed in short or long-term rat studies.

13 Literature

There have been no literature articles citing ZB3579 during the period under review.

In October, results from a nested case-control study of marketed acid-reducing agents were published (Smith J et al 2009). The study showed that current use of proton pump inhibitors was associated with an increased risk of bacterial gastroenteritis compared with non-use, regardless of the treatment duration (relative risk: 2.6; 95% confidence interval: 2.1-3.2), whereas no association was observed with H₂ receptor antagonists (RR: 1.2; 95% CI: 0.8-1.5).

Campylobacter (n=4253) and *Salmonella* (n=1956) were the two species most frequently responsible for gastroenteritis episodes in the case group. Risk ratio calculations on other bacteria related to gastroenteritis could not be made due to the limited number of cases (*Shigella*, n=276 and *C.difficile*, n=28). The results from this study reflect text already present within the product labelling for proton pump inhibitors, to the effect that treatment with acid-reducing drugs may lead to slightly increased risk of gastrointestinal infections such as *Salmonella* and *Campylobacter*.

The relevance of these findings for ZB3579 is unknown. However, if the above findings are related to effective reductions in acid secretion, it may be anticipated that similar findings could become evident in patients treated with ZB3579 in due course.

14 Other DSURs

Zoboryn is not aware of any clinical trials being conducted on ZB3579 by any other organisations.

15 Lack of Efficacy

This section is not applicable, as ZB3579 is not intended for the treatment of serious or life-threatening illness.

16 Region-Specific Information

Appendices R1-R7 provide information meeting local requirements, as follows:

- R1 Cumulative summary tabulation of serious adverse reactions
- R2 List of subjects who died during the reporting period
- R3 List of subjects who dropped out of clinical trials during the reporting period
- R4 Significant Phase I protocol modifications with respect to a US IND
- R5 Significant manufacturing changes
- R6 Description of the general investigation plan for the coming year with respect to a US IND
- R7 Log of outstanding business with respect to a US IND

17 Late-Breaking Information

After the data lock point of this DSUR, Zoboryn received an initial case report of ‘hepatitis’ in a 57 year old woman administered ZB3579 20 mg once daily for 9 weeks for the treatment of GERD (3579DD/015/005/012). The woman was also receiving an unspecified statin for the treatment of hyperlipidaemia. The investigator reported the event as being possibly related to study drug. Follow up information is being sought, in order to clarify the clinical details and the possible role of ZB3579 in this event.

18 Overall Safety Assessment

18.1 Evaluation of the Risks

18.1.1 Possible adverse reactions

A small number of possible adverse reactions has been identified following analysis of the completed Phase II studies (nausea, abdominal pain, flatulence, diarrhoea and skin rash); headache was previously identified during the Phase I programme. The reactions appear to be dose-related and are usually mild in nature, although headache was severe often enough to be considered the dose-limiting effect in the single and multiple ascending dose studies in healthy volunteers. Most of the adverse reactions have resolved with continued therapy, although in some cases skin rash required cessation of therapy before resolution occurred.

Following receipt of a case report of erythema multiforme (see Section 8.1), the Phase III clinical trial data are being closely monitored for reports of possible severe skin reactions, with detailed follow up of any such reports in order to determine their clinical characteristics.

18.1.2 Irritability

Irritability had been observed in a prior 28-day dog study but not observed in a subsequent 12-month dog study, conducted during the period of this DSUR (see Section 12.3). There were no reports of irritability in either of the completed clinical dose-ranging studies, or other evidence of central nervous system effects. As a result, ‘irritability’ is no longer considered a potential risk in patients administered ZB3579.

18.1.3 Liver findings

Results from a recently completed 12-month dog study indicate that ZB3579 may be associated with mild inflammation of canine livers (see Section 12.2).

In the Phase I studies, 253 healthy subjects received ZB3579 as single doses (up to 160mg) and multiple doses for up to ten days (up to 80mg daily). In addition, 286 patients received ZB3579 (up to 40 mg daily) for 14 days. Evaluation of liver function tests (LFTs) in these studies did not reveal any clinically significant elevations likely to be attributed to ZB3579. Relatively minor (<2 times upper limit of normal (ULN)) reversible increases of ALT and aspartate aminotransferase (AST) were observed in some individuals in the ZB3579 and placebo study groups - these were attributed to factors other than exposure to ZB3579.

In the completed Phase II dose-finding studies, patients with GERD were treated for up to 6 weeks with 5-40 mg ZB3579 or 40 mg esomeprazole daily. Liver function tests were performed at 1, 2 and 6 weeks during the dosing period, and 2 weeks following completion of the study. Fluctuations in LFT levels were observed but there were no overall trends of elevations of the liver enzymes observed during the treatment period for any treatment group. Eight individuals administered ZD3579 demonstrated ALT-values >3xULN, none with associated elevations in bilirubin levels; two patients administered esomeprazole demonstrated ALT values >3xULN. Evaluation of the data indicates that there are reasonable clinical explanations other than the study medication in all patients with ALT>3xULN (e.g., alcohol intake, infectious mononucleosis, concomitant medications, elevated values already before dosing, normalized values during continuous medication).

Although liver disorders were not apparent during the Phase I/II clinical trial programme, the duration of therapy in most patients was relatively short and therefore likely to be inconclusive with regards to clinical effects in this regard. It is anticipated that the Phase III programme, with ZB3579 administered for up to 12 weeks, will provide substantive data with regards to any effect of ZB3579 on the liver in man, thereby placing the dog findings into clinical context. Nevertheless, the Phase III trial protocols have been amended to take into account the dog findings and manage any potential risk to patients engaged in these trials:

1. Additional exclusion criteria: patients with prior or current liver disorders, and patients with ALT>1.5xULN or bilirubin>ULN

2. Frequent monitoring of LFTs, with individual stopping rules. In the three ongoing Phase III 12-week studies, patients now have LFTs measured at 1, 2, 4, 8 and 12 weeks, and 2 weeks post-dosing. In addition, patients are advised to see their investigator immediately if they have any signs or symptoms suggestive of liver disorder (e.g., anorexia, nausea, vomiting, right upper quadrant pain, fatigue, lethargy, flu-like symptoms, pruritus and jaundice). A case handling plan within each trial protocol now specifies that an elevation of ALT, AST or alkaline phosphatase (ALP) of $>3xULN$ in any patient should elicit an alert fax from the central laboratory to the ZB3579 study team and the investigator. Such a patient will be called back to the clinic within three days from the time when the test results are acknowledged, for additional laboratory screening and continuous monitoring, physical examination and medical history focusing on reasons for the LFT abnormality and, if needed, further investigation. The study medication will be withdrawn immediately if ALT, AST or ALP is $>5xULN$, or if the total bilirubin is $>2xULN$ in combination with elevations in any of ALT, AST or ALP $>3xULN$.

Based on the preclinical studies in dogs, sustained elevations of ALT seem to be a reliable marker of liver abnormality preceding the development of histopathological changes. Thus, diligent application of the handling plan for elevated LFTs should ensure the safety of the patients participating in the ongoing trials.

Finally, Zoboryn has established a Data Monitoring Committee to oversee the safety of patients participating in the three Phase III clinical trials. Laboratory and adverse event data are provided to the Committee as and when received by Zoboryn. The Committee has access to their own copies of the randomisation codes so that they can evaluate the ongoing data in an open fashion. The Committee will provide monthly reports to Zoboryn as to whether or not there is any indication of adverse effects upon the liver in clinical trial participants.

Data Monitoring Committee activities are supplemented by on-line weekly assessment of the liver laboratory values for the whole study population by the ZB3579 Global Safety Physician and the Clinical Study Team Physician, with the study blind maintained. The ZB3579 clinical team will contact the Data Monitoring Committee in the event that unexplained abnormalities are detected by this in-house review, for the Data Monitoring Committee to consider a further unblinded assessment.

18.1.4 Pancreatitis

Three case reports of pancreatitis have now been received during the course of ZB3579 clinical trials, two during Phase II (see Section 8.1) and one during the ongoing Phase III programme (see Section 8.2). In each of the three cases, there are plausible alternative explanations and a causal relationship with ZB3579 has not been determined. Nevertheless, this topic will be kept under review as the Phase III programme progresses, with immediate attention given to any additional case reports of pancreatitis.

18.1.5 Potential interactions

Human drug metabolism studies indicate that ZB3579 has no effect on cytochrome P450 enzymes, such that the clinical pharmacokinetics of ZB3579 are unlikely to be affected by P450 inducers or inhibitors. However, an antacid interaction study, conducted prior to the reporting period, demonstrated that co-administration of antacids may decrease the bioavailability of ZB3579, and the current clinical trial protocols require that ZB3579 should be taken at least 2 hours before or after taking antacids.

Many patients with GERD take non-steroidal anti-inflammatory drugs (NSAIDs) for concurrent disorders. To date, no clinically significant interactions of ZB3579 with NSAIDs have been demonstrated. Although no formal interactions studies have been performed in this regard, the potential for interaction with NSAIDs will be evaluated as part of the ongoing Phase III clinical trial programme.

18.2 Benefit-Risk Considerations

ZB3579 is currently being investigated for the treatment of adults with GERD as its primary indication. It is anticipated that it will differ from established therapies (proton pump inhibitors and H₂-antagonists) with faster, more complete and longer-lasting suppression of gastric acid, thereby improving the effectiveness of the treatment of GERD.

During the reporting period, Zoboryn analysed data from two completed dose-ranging clinical trials (3579DD/0013 and 3579DD/0014) investigating ZB3579 in the treatment of GERD when given for 6 weeks. The data indicate that ZB3579 suppresses gastric acid effectively in patients with GERD, leading to improvement in endoscopic findings and symptoms, sufficient

to support a decision to initiate a Phase III clinical trial programme with esomeprazole and lansoprazole as active comparators.

The identification of GI symptoms and skin rash as possible adverse reactions does not impact upon the anticipated favourable benefit-risk profile for ZB3579, and they do not necessitate any amendment to existing clinical study protocols or informed consent forms.

The eventual clinical implications of the liver findings in dogs has yet to be determined; the risk to individual patients participating in ZB3579 clinical trials is being managed through instigation of enhanced LFT monitoring and stopping rules, with oversight of ongoing data by a Data Monitoring Committee.

Pancreatitis and severe skin reactions have been identified as items to monitor closely as the Phase III programme progresses.

19 Summary of Important Risks

This section summarises the important identified or potential risks that have been recognised during the conduct of the ZB3579 clinical trial programme. The following have been recognised as important potential risks during the reporting period:

- Liver toxicity
- Pancreatitis
- Severe skin reactions

Further details are provided in Table 2.

Table 2 Summary of Prior and Ongoing Important Risks

Potential Risk	Preclinical data	Clinical data	Actions
Irritability	28-day dog study: irritability in moderate-dose dogs. 12-month dog study: irritability not observed at same dose. Rat studies: irritability not observed.	Phase I-II clinical studies: irritability not observed. <u>No longer considered a potential risk.</u>	The status of this potential risk will be confirmed by the outcome of ongoing Phase III clinical trials.

Liver toxicity	12-month dog study: ZB3579 may be associated with mild hepatic inflammation.	Phase I-II clinical studies: liver injury not evident.	The relatively short duration of therapy in Phase I/II studies means that longer duration clinical studies are necessary to place the dog findings into context. Phase III clinical trial protocols have been amended to manage potential risk of liver injury to trial subjects: <ul style="list-style-type: none"> • additional exclusion criteria • enhanced LFT monitoring • stopping rules • Data Monitoring Committee established
Pancreatitis	No findings.	Three case reports of pancreatitis reported. Causal relationship with ZB3579 not determined - plausible alternative explanations for each case.	This topic to be kept under review as the Phase III programme progresses - immediate attention will be given to any further case reports.
Severe skin reactions	No findings.	Phase II trials indicate that patients may experience skin rash when administered ZB3579. Single case of erythema multiforme reported in a Phase II trial.	Phase III clinical trials are being closely monitored for reports of severe skin reactions (e.g., erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis), with detailed follow up of any affected patients.

Identified Risks	Preclinical data	Clinical data	Actions
None identified	Not applicable	Not applicable	Not applicable

20 Conclusions

Headache, nausea, abdominal pain, flatulence, diarrhoea and skin rash have been identified as adverse drug reactions following a review of Phase II clinical trial data.

Liver toxicity, pancreatitis and severe skin reactions have been identified as important potential risks, to be closely monitored as the Phase III clinical programme progresses.

Phase III trial protocols have been amended to manage any risk of liver injury to trial subjects, with additional exclusion criteria, enhanced LFT monitoring, stopping rules and Data Monitoring Committee oversight.

The potential risks identified in association with ZB3579 are justified by the anticipated benefits that may be afforded to patients with GERD.

APPENDIX 1

INVESTIGATOR'S BROCHURE

The following are attached to this DSUR:

ZB3579 IB dated 1st December 2009

APPENDIX 2

CUMULATIVE TABLE OF IMPORTANT REGULATORY REQUESTS

Date	Agency/country	Request	Status
25-Nov-2007	FDA/USA	Holter monitoring required in US Phase II clinical trial (3579DD/014)	Study completed – no significant findings

APPENDIX 3

STATUS OF ONGOING AND COMPLETED CLINICAL TRIALS

APPENDIX 3A ONGOING CLINICAL TRIALS

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	FVFP*	Planned enrolment	Subject exposure**
3579DD/016	III	Europe	Assessment of safety and efficacy in patients with GERD	Randomised, double-blind, parallel, active-controlled	ZB3579 10-20 mg or esomeprazole 40 mg po od 12 weeks	Males/females Age: 18-90 GERD patients	2/8/09	ZY 10 mg: 500 ZY 20 mg: 500 Esomeprazole: 500	ZY 10 mg: 136 ZY 20 mg: 136 Esomeprazole: 136
3579DD/017	III	USA Canada	Assessment of safety and efficacy in patients with GERD	Randomised, double-blind, parallel, active-controlled	ZB3579 10-20 mg or esomeprazole 40 mg po od 12 weeks	Males/females Age: 18-90 GERD patients	3/8/09	ZY 10 mg: 500 ZY 20 mg: 500 Esomeprazole: 500	ZY 10 mg: 145 ZY 20 mg: 145 Esomeprazole: 145
3579DD/018	I	UK	Renal impairment study	Randomised, double-blind, parallel	ZB3579 10 mg od po 7 days	Males/females Age: 18-65 Renally impaired patients	4/12/09	ZB3579: 18	ZB3579: 12
3579DD/019	I	UK	Hepatic impairment study	Randomised, double-blind, parallel	ZB3579 10 mg od po 7 days	Males/females Age: 18-65 Hepatically impaired patients	24/11/09	ZB3579: 18	ZB3579: 8
3579DD/020	III	Europe	Assessment of safety and efficacy in patients with GERD	Randomised, double-blind, parallel, active-controlled 12 weeks	ZB3579 10-20 mg or lansoprazole 30 mg po od 12 weeks	Males/females Age: 18-90 GERD patients	13/9/09	ZY 10 mg: 500 ZY 20 mg: 500 Lansoprazole: 500	ZY 10 mg: 56 ZY 20 mg: 56 Lansoprazole: 56
3579DD/021	I	UK	Bioavailability study (Phase II vs III formulations)	Randomised, double-blind, cross-over	ZB3579 10-20 mg po sd (x2 formulations)	Males Age: 18-45 Healthy volunteers	5/12/09	ZB3579: 12	ZY 10 mg: 6 ZY 20 mg: 6

* FVFP = first visit first patient

** based upon total number of patients recruited as of 31st December 2009 and applied randomisation schemes

APPENDIX 3B CLINICAL TRIALS COMPLETED DURING THE REPORTING PERIOD

Study ID	Phase	Country	Study Title	Study design	Dosing regimen	Study population	Subject exposure
3579DD/013	II	Europe	Dose-response study of safety and efficacy in patients with GERD	Randomised, double-blind, parallel, active-controlled 6 weeks	ZB3579: 5-40 mg po od Esomeprazole: 40 mg po od	Males/females Age: 18-90 GERD patients	ZY 5 mg: 224 ZY 10 mg: 236 ZY 20 mg: 228 ZY 40 mg: 219 Esomeprazole: 225
3579DD/014	II	USA Canada	Dose-response study of safety and efficacy in patients with GERD	Randomised, double-blind, parallel, active-controlled 6 weeks	ZB3579: 5-40 mg po od Esomeprazole: 40 mg po od	Males/females Age: 18-90 GERD patients	ZY 5 mg: 186 ZY 10 mg: 192 ZY 20 mg: 182 ZY 40 mg: 198 Esomeprazole: 184

APPENDIX 4

CUMULATIVE SUMMARY TABULATIONS OF DEMOGRAPHIC DATA

Table 1 Estimated Cumulative Subject Exposure to ZB3579 in all Clinical Studies by Age and Sex*

Age (yr)	Number of Subjects		
	Male	Female	Total
<18	0	0	0
18 - 65	1075	771	1846
66 – 75	169	211	380
>75	6	12	18
Total	1250	994	2244

* data from completed studies as of 31st December 2009

Table 2 Estimated Cumulative Subject Exposure to ZB3579 in all Clinical Studies by Racial Group*

Racial group	Number of Subjects
Caucasian	1779
Black	392
Asian	59
Other	14
Unknown	0
Total	2244

* data from completed studies as of 31st December 2009

APPENDIX 5 LINE LISTING OF SERIOUS ADVERSE REACTIONS

SOC: Immune System Disorders

Trial number [EudraCT # ¹]	Case ID/ Subject # ²	Country Gender Age	Serious ADR(s)	Outcome ³	Date of Onset ⁴ Time to Onset ⁴	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
3579DD/013 [2007-001234-56]	2009UK01234 013/012/005	UK F 56y	Allergic reaction Rash Oedema Hypotension	Resolved	15-Mar-09 14d	ZB3579	20 mg po tablet	02-Mar-09 - 15-Mar-09 14d	Hospitalised. Diagnosis of drug allergy. Time to onset 2 wks from first dose of ZB3579 and 3d from first dose of amoxicillin (chest infection). Investigator considers the event possibly related to ZB3579 and/or amoxicillin.

SOC: Metabolism and Nutrition

Trial number [EudraCT # ¹]	Case ID/ Subject # ²	Country Gender Age	Serious ADR(s)	Outcome ³	Date of Onset ⁴ Time to Onset ⁴	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
3579DD/014 [n/a]	2009US04321 014/010/003	USA F 78y	Hyponatraemia	Resolved	26-Feb-09 24d	ZB3579	10 mg po tablet	2-Feb-09– 26-Feb-09 24d	Hospitalised. History of hypercholesterolaemia, hyperuricaemia and diabetes. Multiple concomitant medications. Investigator considers ZB3579 and Altizide/Spironolactone as co-suspect drugs.
etc	etc	etc	etc	etc	etc	etc	etc	etc	etc

- 1 EudraCT number – if applicable
- 2 Subject number: study/centre/patient
- 3 Case level (e.g., resolved, fatal, improved, sequelae, unknown)
- 4 ‘Primary’ serious ADR only

APPENDIX 6

CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE EVENTS

<u>System Organ Class</u>	ZB3579	Total up to 31-Dec-09		
		Blinded	Active Comparator	Placebo
Preferred term				
<u>Blood and lymphatic system disorders</u>				
Thrombocytopenia	0	2	1	0
Leukopenia	1	0	1	0
<u>Cardiac disorders</u>				
Angina pectoris	0	1	0	0
Myocardial infarction	1	0	1	0
Ventricular tachycardia	0	1	0	0
<u>Gastrointestinal disorders</u>				
Abdominal pain	3	2	2	0
Pancreatitis	2	1	0	0
etc	etc	etc	etc	etc

APPENDIX 7

SCIENTIFIC ABSTRACTS

No presentations relevant to ZB3579 were made during the period under review.

APPENDIX R1

CUMULATIVE SUMMARY TABULATION OF SERIOUS ADVERSE REACTIONS

<u>System Organ Class</u>	ZB3579	Total up to 31-Dec-09		
		Blinded	Active Comparator	Placebo
Preferred term				
<u>Blood and lymphatic system disorders</u>				
Thrombocytopenia*	0	1	1	0
<u>Gastrointestinal disorders</u>				
Abdominal pain*	1	2	1	0
Pancreatitis*	1	0	0	0
etc	etc	etc	etc	etc

* denotes unexpected term

APPENDIX R2

LIST OF SUBJECTS WHO DIED DURING THE REPORTING PERIOD

Trial number [EudraCT #¹]	Case ID/ Subject #²	Country Gender Age	Cause of Death	Date of Onset³ Time to Onset³	Suspect Drug	Daily dose Route Formulation	Dates of treatment Treatment duration	Comments
3579DD/013 [2007-001234-56]	2009UK01256 013/034/019	UK M 57y	Myocardial infarction	18-Mar-09 5 weeks	ZB3579	20 mg po	11-Feb-09 – 18-Mar-09 5 weeks	Collapsed while shopping. History of type 2 diabetes, hyperlipidaemia, coronary heart disease. Investigator considers the event unrelated to study therapy.
3579DD/015 [n/a]	2009US02345 015/011/001	USA F 62y	Septicaemia Multiorgan failure	1-Oct-09 4 weeks	Blinded	Blinded	3-Sep-09 – 14-Oct-09 6 weeks	Breast cancer diagnosed 12 Sept 09. Septicaemia and multiorgan failure followed post-operative wound infection (radical mastectomy). BMI 35 kg/m ² . Investigator considers the event unrelated to study therapy.

- 1 EudraCT number – if applicable
- 2 Subject number: study/centre/patient
- 3 ‘Primary’ serious ADR only

APPENDIX R3

LIST OF SUBJECTS WHO DROPPED OUT OF STUDIES DURING THE REPORTING PERIOD

Sixty eight patients dropped out in association with adverse events during the reporting period. Of these, 55 patients were administered ZB3579 (5 at 5 mg, 9 at 10 mg, 11 at 20 mg and 30 at 40 mg) and 13 patients received esomeprazole. Eighteen patients were withdrawn due to serious adverse events; twelve patients received ZB3579, five received esomeprazole and one received lansoprazole.

The most common adverse events leading to withdrawal were non-serious in nature, most often gastrointestinal symptoms, headache or skin rash.

Details of the adverse events leading to withdrawal during the period under review are presented in the table below, with the SAEs highlighted in bold.

TABLE R3

SUBJECTS WHO DROPPED OUT OF STUDIES DURING THE REPORTING PERIOD

SOC: Immune system disorders

Trial number [EudraCT #¹]	Case ID/ Subject #²	Country Gender Age	Adverse Event(s)	Study Drug	Comments
3579DD/013 [2007-001234-56]	2009UK01234 013/012/005	UK F 56y	Allergic reaction Rash Oedema Hypotension	ZB3579	Hospitalised. Diagnosis of drug allergy. Time to onset 2 wks from first dose of ZB3579 and 3d from first dose of amoxicillin (chest infection). Investigator considers the event possibly related to ZB3579 and/or amoxicillin.

SOC: Gastrointestinal disorders

Trial number [EudraCT #¹]	Case ID/ Subject #²	Country Gender Age	Adverse Event(s)	Study Drug	Comments
3579DD/013 [2007-001234-56]	2009FR00154 013/002/023	France F 52y	Pancreatitis	ZB3579	Possible alcohol abuse during preceding week. Medical history includes hyperlipidaemia and Type 2 diabetes. Concomitant medications include simvastatin and metformin. Investigator considers the event possibly related to ZB3579 or simvastatin.
etc	etc	etc	etc	etc	etc

1 EudraCT number – if applicable

2 Subject number: study/centre/patient

APPENDIX R4
SIGNIFICANT PHASE I PROTOCOL MODIFICATIONS WITH RESPECT TO
A US IND

There were no modifications to Phase I protocols relating to a US IND during the reporting period.

APPENDIX R5
SIGNIFICANT MANUFACTURING CHANGES

The manufacturing process was 'scaled up' during 2009 so that ZB3579 could be produced in sufficient quantities for the Phase III clinical trial programme. As part of this change, it was necessary to add metacrylic acid co-polymer as an excipient in order to facilitate production of material in the bulk necessary for large-scale clinical trials, and the anticipated market launch.

It is not anticipated that the addition of metacrylic acid co-polymer will alter the pharmacokinetic or pharmacodynamic properties of ZB3579. Because the change in the manufacturing process was finalised relatively late, it was not possible to confirm this before initiation of the Phase III clinical programme. A PK/PD bioavailability study (3579DD/021), comparing the Phase II and III formulations in healthy volunteers, is currently in progress.

APPENDIX R6

DESCRIPTION OF THE GENERAL INVESTIGATION PLAN FOR THE COMING YEAR WITH RESPECT TO A US IND

Enrolment into the three Phase III clinical trials (3579DD/016, 3579DD/017 & 3579DD/020) will continue throughout the coming year - it is anticipated that enrolment will be completed during early 2011.

Three Phase I studies will be completed during 2010 (3579DD/018 - renal impairment; 3579DD/019 – hepatic impairment; 3579DD/021 – bioavailability) and clinical study reports will be provided accordingly.

We are planning to submit a new IND for ZB3579 for the treatment of peptic ulcer disease in late 2010; we are planning to request a pre-IND meeting in the near future.

APPENDIX R7

LOG OF OUTSTANDING BUSINESS WITH RESPECT TO A US IND

There is no outstanding business with respect to a US IND for which the sponsor requests or expects a reply, comment or meeting.