# INNOVATIVE PHARMACEUTICAL BIOTECH LIMITED
# 領航醫藥及生物科技有限公司

*(Incorporated in the Cayman Islands and continued in Bermuda with limited liability)*

**(Stock Code: 399)**

## BUSINESS UPDATE
## UPDATES ON THE STATUS OF COMMERCIALIZATION OF THE PRODUCT

References are made to (i) the joint announcement issued by Extrawell Pharmaceutical Holdings Limited and Innovative Pharmaceutical Biotech Limited (the "**Company**", together with its subsidiaries, the "**Group**") dated 18 March 2014 in relation to, among others, the acquisition (the "**Acquisition**") of 51% of the issued share capital of Smart Ascent Limited ("**Smart Ascent**") by the Group; (ii) the circular of the Company dated 26 June 2014 in relation to the Acquisition; and (iii) the announcements of the Company dated 9 January 2018, 15 August 2018, 14 September 2018 and 14 November 2018 in relation to, among others, the status of the commercialization of the oral insulin product (the "**Product**").

## UPDATES ON THE STATUS OF COMMERCIALIZATION OF THE PRODUCT

This announcement is made by the Company to keep the shareholders and potential investors of the Company informed of the latest business development of the Group with regards to, among others, (i) the details of phase III of the clinical trial, including the procedures and actions taken and/or to be taken; (ii) timetable for commercialization of the Product; (iii) the details of the market opportunity of the Product and its market competitiveness; and (iv) reasons for the repeated delays in the timetable for the development of the Product.

**The details of Phase III of the Clinical Trial**

Phase III of the clinical trial consists of two parts. Part A of phase III of the clinical trial relates to the multi-centered, randomised, double-blinded and placebo controlled clinical trial of the Product on treatment of Type 2 diabetes. Part B of phase III of the clinical trial (the "**Clinical Trial**") involves extended clinical trial with more extensive sampling of the Product.

Part A of phase III of the clinical trial had been completed in 2013 with satisfactory results. The progress and results of the clinical trials up-to-date indicated that the Product achieved positive effect, in particular, the statistical outcome of the per-protocol set (PPS) analysis relating to part A of phase III of the clinical trial shows that the bio-efficacy of the Product in the treatment group was significantly superior to that of the control group in the effect of reducing blood glucose level in diabetics.

In respect of Phase III of the clinical trial, the State Food and Drug Administration imposed more stringent requirements which include a requirement for a larger sample group of patients, and the use of double-blind tests where neither the patents nor the researchers have knowledge on which patients belong to the treatment group (where patients will be given the Product) or the control group (where patients will be given placebo), with a view to reducing experimental bias during phase III of the clinical trial.

With regards to the material communication with the regulatory authorities, the proposal of the Clinical Trial had previously been submitted to the relevant authorities for drug evaluation and the application status of the Clinical Trial was registered with the National Medical Products Administration (the "**NMPA**") in October 2019. The Group and its representatives have also verbally communicated with the relevant regulatory authorities in relation to the latest revised plan of the Clinical Trial. As at the date of this announcement, the Group has completed the design of the Clinical Trial and is currently in the process of selection and enrolment of patients as well as selection of hospitals.

Details of the Clinical Trial based on the 胰島素腸溶膠丸III期臨床試驗方案 (transliterated as the protocol for phase III of the clinical trial for insulin enteric-coated soft capsule) (the "**Protocol**") is set out below:

***Objective of the trial***

According to the Protocol, the main objective of the Clinical Trial is to evaluate with reference to their respective baseline level, the change in glycated hemoglobin value of the experimental group, comprising type 2 diabetes patients with poor glycemic control, after being administered with the Product combining with oral antidiabetic drugs ("**OADs**") for 24 weeks as compared with the results for the placebo group combining with OADs.

The secondary objectives of the Clinical Trial include the following:

(i) to evaluate with reference to their respective baseline level, the change in glycated hemoglobin value of the experimental group after being administered with the Product combining with OADs for 24 weeks as compared with the results for the positive control group combining with OADs;

(ii) to evaluate with reference to their respective baseline level, the change in glycated hemoglobin value of the experimental group after being administered with the Product combining with OADs for 12 weeks as compared with the results for the positive control group combining with OADs and placebo group combining with OADs respectively;

(iii) to evaluate the proportion of subjects from the experimental group that had glycated hemoglobin level (a) less than or equal to 7.0%; and (b) less than or equal to 6.5%, after being administered with the Products combining with OADs for 24 weeks as compared with the results for the positive control group combining with OADs and placebo group combining with OADs respectively;

(iv) to evaluate with reference to their respective baseline level, the change in the fasting venous blood glucose level of the experimental group after being administered with the Product combining with OADs for 24 weeks as compared with the results for the positive control group combining with OADs and placebo group combining with OADs respectively;

(v) to evaluate with reference to their respective baseline level, the change in postprandial glucose level 2 hours after the meal tolerance test of the experimental group after being administered with the Product combining with OADs for 24 weeks as compared with the results for the positive control group combining with OADs and placebo group combining with OADs respectively; and

(vi) to evaluate the safety and patient satisfaction level of subjects from the experimental group with regards to the diabetes treatment after being administered with the Products combining with OADs for 24 weeks.

***Design of the trial, including duration, method of experimental controls and dosage study***

The Clinical Trial will comprise of three groups with a total of 650 subjects, of which 390 (oral insulin enteric-coated soft capsules) will be placed in the experimental group, 130 (recombinant insulin glargine injection) will be placed in the positive control group and 130 will be placed in the placebo group.

The 650 subjects selected for the trial will all be type 2 diabetes patients. Subjects who pass the preliminary screening will be placed in one of the three groups. The selection process will take approximately 2 weeks.

All of the selected subjects will continue to be administered OADs during the trial based on their previous dosage. At the same time, the three groups will be administered with the Product, the placebo or insulin injection based on their respective mode of administration. The starting dosage for the experimental group and the placebo group will be 4 oral insulin enteric-coated soft capsules or placebo (as the case may be), each at approximately 1 to 1.5 hours before breakfast and dinner during the dose adjustment period (the "**Dose Adjustment Period**"), which takes place from the first day of the Clinical Trial up to the end of week 4. The positive control group will be injected with recombinant insulin glargine every night at approximately 8:00 p.m. to 10:00 p.m. during the Dose Adjustment Period, with starting dosage of approximately 0.2U/kg/d. During the Dose Adjustment Period, the clinicians will make dose adjustments based on the subject's blood glucose testing on a weekly basis. During the fixed dosed period (the "**Fixed Dose Period**"), which takes place from the start of week 5 up to the end of week 24, subjects will take medication according to the dosage determined during the Dose Adjustment Period and no further dose adjustment will be performed.

The subjects will need to continuously monitor blood glucose from the first day of receiving medication until the end of follow-up in week 24. In particular, the subjects will need to monitor their blood glucose at least 2 days a week during the Dose Adjustment Period (preferably 3 days before the visit and on the day of each visit). The experiment group and the placebo group will need to monitor both their early fasting plasma glucose and pre-dinner blood glucose on the same day. The positive control group will only need to monitor their early fasting plasma glucose on each occasion. During the Fixed Dose Period, all subjects will need to measure their early fasting plasma glucose at least once a week. The Clinical Trial will take approximately 24 weeks. During the Clinical Trial, the subjects will be prohibited from taking any other OADs not included in the Protocol.

***The formulation of the trial plans, the determination of the method of experimental controls and dosage study***

The Group has entered into a technical service agreement with the contract research organisation (the "**CRO**") on 31 October 2018 pursuant to which the CRO will be responsible for coordinating, supervising and managing the whole process of the clinical research in respect of the Product to ensure its authenticity, standardisation and integrity in accordance with the relevant requirements of the PRC laws and regulations.

The CRO is a company established in the People's Republic of China (the "**PRC**") with limited liability and is principally engaged in, among others, medical new technology development and transfer, medical technology service, medical consultation service and clinical medical research.

Following various discussions between the project team comprising of the CRO, the Group and Jiangsu Hospital, the CRO has prepared the Protocol in or around April 2019. The Protocol sets out, among others, the objective as well as the procedures and actions to be taken in respect of each stage of the Clinical Trial, including but not limited to the formation of the trial plans, the determination of the method of experimental controls and dosage study.

***The selection and enrolment of patient***

Due to the outbreak of the coronavirus since early 2020, the normal operations of the participating hospitals for the Clinical Trial had been severely disrupted. In order to ensure the safety of patients and clinical researchers, research projects such as the Clinical Trial had been temporarily suspended and as result there had been a delay in the selection and enrolment of patients for the Clinical Trial.

Given that there is a large number of participating hospitals, the patients will be divided into different groups. Subject to the coronavirus situation improving, it is currently expected that the enrolment of the first batch of patients will commence in July 2020. The enrolment of patients will be an ongoing process and is expected to be completed during the period from January 2021 to March 2021.

***The selection of hospital***

As at the date of this announcement, The Group has invited 22 hospitals to participate in the Clinical Trial, of which 6 hospitals (including Jiangsu Hospital) have already accepted the invitation whereas the remaining 16 hospitals are still undergoing internal approval procedures required by the respective hospital's ethical committee.

***The execution of clinical trial testing***

The execution of clinical trial testing will be carried out in accordance with the procedures set out in the Protocol. Subject to the coronavirus situation improving, the clinical trial testing for the first group of subjects is expected to commence in August 2020 and will take approximately 24 weeks to complete. Based on the current timetable, all of the 650 subjects are expected to complete the clinical trial testing by the fourth quarter of 2021.

*The data and outcome analysis*

The data and outcome analysis includes the distribution of subject characteristics; primary efficacy endpoint analysis; secondary effectiveness endpoint analysis; safety analysis; subgroup analysis and other analysis. The data and outcome analysis is expected to be completed by fourth quarter of 2021.

*The preparation of the outcome report*

The outcome report is based on the findings of the data and outcome analysis derived from the execution of the clinical trial testing. The preparation of the outcome report is expected to commence in in January 2022 and to be completed by March 2022.

**The details of procedures and actions taken and/or to be taken to commercialise the Product following completion of the Phase III of the Clinical Trial**

*The submission of the clinical trial report to NMPA*

The clinical trial report, which will be based on the results of the Clinical Trial, is expected to be submitted to the NMPA by the end of first quarter of 2022

*The application for the new medicine certificates and manufacturing permit*

After the Clinical Trial is completed, the application for new medicine certificates is expected to be submitted to the NMPA for approval in the end of first quarter of 2022, and the relevant certificate is expected to be obtained by late second quarter of 2022. During the application review process, there will likely be ongoing communications between the CRO and NMPA.

In the meantime, the Group will make the necessary arrangements to ensure that the production facilities will be ready for production. Once the new medicine certificate had been obtained, an application for the manufacturing permit is expected to be made to the pharmaceutical regulatory authority in late second quarter of 2022. The manufacturing permit is expected to be obtained by mid third quarter of 2022.

*General requirements for admission of new drugs*

The admission of new drugs in the PRC is governed by, among others, the Provisions for Drug Registration (藥品註冊管理辦法) (the "**Drug Registration Rule**"). According to the Drug Registration Rule, an application for registration of new drugs refer an application for registration of drugs that have not been marketed within the territory of the PRC, which includes changing dosage form or route of administration, or claiming a new indication for marketed drugs. Other types of registration of drugs include registration of a generic drug or import drug.

Pursuant to the Drug Registration Rule, NMPA will conduct a systematic assessment of the safety, efficacy and quality control aspects in determining whether to approve an application to register a drug. The applicant shall provide sufficient and reliable research data to prove the safety, efficacy and quality of the drug, and be liable for the authenticity of all the dossiers submitted. In particular, clinical trials shall be conducted for new drug registration applications. After completion of a clinical trial, the applicant shall submit a clinical trial final report, a statistical analysis report and its database to NMPA.

*General requirements for grant of pharmaceutical manufacturing permit*

The Regulations for the Implementation of the Drug Administration Law of the PRC (中華人民共和國藥品管理法實施條例) (the "**Regulations**") governs the procedure and timing for application by drug manufactures for the pharmaceutical manufacturing permit.

According to the Regulations, the pharmaceutical manufacturing permit will only be granted if the applicant passes the inspection carried out by the pharmaceutical regulatory authority based on the following conditions for formation prescribed in Article 8 of the Pharmaceutical Administration Law of the PRC (中華人民共和國藥品管理法):

(a) there are qualified pharmaceutical technicians, engineering technicians and relevant skilled workers in accordance with the law;

(b) there are plants, facilities and sanitary environment suitable for its pharmaceutical production;

(c) there is an organisation, personnel and necessary instrument and equipment to ensure quality management and quality inspection of the produced drugs; and

(d) have rules, regulations and system in place to ensure the quality of the drugs.

The pharmaceutical manufacturing permit has a validity of five years. To continue its drug production, the drug manufacturer must apply to the pharmaceutical regulatory authority for renewal of its permit within six months prior to the expiry date of the relevant certificate.

**Timetable for Commercialisation of the Product**

Set out below is the tentative timetable for commercialisation of the Product based on the latest information available:

| **Event/action/milestone** | **Expected completion date** |
|---|---|
| Design of the trial, including duration, method of experimental controls and dosage study | Completed |
| The selection and enrolment of patient | First quarter of 2021 |
| The selection of hospital | First quarter of 2021 |
| The execution of clinical trial testing | Fourth quarter of 2021 |
| The data and outcome analysis | Fourth quarter of 2021 |
| The preparation of the outcome report | First quarter of 2022 |
| The entering into of an agreement in respect of the production arrangement | First quarter of 2022 |
| The sourcing of raw materials from various suppliers for production of the Product | First quarter of 2022 |
| Possible marketing activities or pre-sales preparation work | First quarter of 2022 |
| The submission of the clinical trial report to NMPA | End of first quarter of 2022 |
| The application for the new medicine certificates | End of first quarter of 2022 |
| The obtaining of the new medicine certificates | Late second quarter of 2022 |
| The application for the manufacturing permit | Late second quarter of 2022 |
| The obtaining of the manufacturing permit | Mid third quarter of 2022 |
| The Product is launched in the market and available for sale at selected hospital | Fourth quarter of 2022 |

**The details of the market opportunity of the Product and its market competitiveness**

According to the IDF Diabetes Atlas (8th Edition) (the "**Report**") issued by the International Diabetes Federation in 2017, diabetes is a prevalent chronic disease affecting approximately 424.9 million people around the world in 2017, representing approximately 8.8% of the total population in the world. As set out in the Report, it is estimated that the PRC accounted for approximately 114.4 million people with diabetes in 2017 with the number of diabetes patients rising to approximately 119.8 million by 2045. In terms of healthcare expenditure, the PRC incurred an estimated US$110 billion in total healthcare expenditure on diabetes in 2017 (20–79 years). In view of the above, there is an enormous market in the PRC for the Product, which provides superior and effective treatment for the growing diabetic population in the PRC.

The insulin drugs that are currently generally available in injection form. The Product enables insulin delivery by an oral route which is considered, compared with injection, to be a more convenient, safer and painless way of administration, thus facilitating better patient compliance and can also help improving quality of life of patients. Hence, the Company considered that the Product will have a competitive advantage over existing insulin drugs in the market.

**Reasons for the repeated delays in the timetable for the development of the Product**

Set out in the table below are reasons for the repeated delays in the timetable for the development of the Product.

| | Event | Duration |
|---|---|---|
| 1. | The Group spent time on revisiting the feasibility as well as the cost and benefit analysis of carrying out the research and development of the Product in the United States (the "**US**") and/or the European Union (the "**EU**"). After further analysis and consideration taking into account the results of the feasibility study and the time and costs involved, the management decided not to proceed with the EU/US approval route. | From July 2014 to the end of 2015 |
| 2. | The Company had been exploring and discussing with potential investors and business partners in relation to possible cooperation in the joint development of the Product. The Company believed that with the support from investors and business partners, the project will have a greater chance of success as the Group can benefit from their customer network, reputation in the market and financial resources in the development and marketing of the Product.<br><br>Hence, the progress of the Clinical Trial was slowed down during the relevant period in order to provide room for the fine-tuning of the forms of co-operation with the potential investors that can bring the greatest benefits to the project and the Group. | From July 2014 to 2017 |
| 3. | The Group worked with the former contract research organization and other clinical experts to revise the plan of the Clinical Trial in light of the change from the EU/US approval route to the direct China Food and Drug Administration (the "**CFDA**") approval route, which included, redesigning the methodology of the tests for the Clinical Trial, determining the number of samples for those tests, determining the number of hospitals, determining the sample size for each hospital and finalizing the costs and budget of the Clinical Trial.<br><br>The Group also spent time to communicate with the CFDA for the revised plan, to search for potential hospitals which would be involved in the conducting of the Clinical Trial and to recruit supervisors to monitor the progress of the project. | From the end of 2015 to 2017 |
| 4. | The Group was in the process of identifying and selecting (i) a contract research organization, who will be responsible for coordinating, supervising and managing the whole process of the clinical research of the Product; and (ii) a principal investigator, who will lead the conduct of the Clinical Trial. | From 2016 to end of 2018 |

| | Event | Duration |
|---|---|---|
| 5. | Due to certain restructuring of the relevant organization of experts which slowed down the communication process, the Company has spent more time to revise and finalize the plan of the Clinical Trial in accordance with the latest clinical guidelines for diabetes treatment. Further, additional time has been spent to ensure that the Clinical Trial will be able to demonstrate efficacy and superiority of the Product relative to similar drugs in the market. | From mid-2017 to 2019 |
| 6. | The Group confirmed the engagement of the contract research organization and the principal investigator as well as finalized the design of the trial, including duration, method of experimental controls and dosage study. | From 2018 to 2019 |
| 7. | Due to the outbreak of the coronavirus, the commencement of the Clinical Trial for the selection and enrollment of the first group of patients, which was originally scheduled to take place in February 2020, was temporarily suspended. | Since February 2020 |

By Order of the Board
**Innovative Pharmaceutical Biotech Limited**
**Tang Rong**
*Executive Director*

Hong Kong, 20 May 2020

*As at the date of this announcement, the Board comprises Ms. Jiang Nian (chairman & non-executive director), Mr. Gao Yuan Xing (executive director), Mr. Tang Rong (executive director), Ms. Huang He (executive director), Ms. Xiao Yan (non-executive director), Ms. Wu Yanmin (non-executive director), Ms. Chen Weijun (independent non-executive director), Dr. Zhang Zhihong (independent non-executive director) and Mr. Wang Rongliang (independent non-executive director).*