Main Informed Consent Form
And Authorization to Use and Share Your Protected Health Information

Study Lay Title:	A study to test whether different doses of BI 456906 are effective in treating adults with type 2 diabetes.
Sponsor:	Boehringer Ingelheim Pharmaceuticals, Inc.
Protocol No.:	1404-0002
Study Doctor:	Anuj Bhargava, MD Iowa Diabetes and Endocrinology Research Center, PLC 1031 Office Park Rd, Suite 2 West Des Moines, IA 50265
Telephone:	515-329-6800
24-Hour Contact Number:	515-329-6800

Study Subject Number: _____

You are being asked to join this clinical research study, referred to in this consent form as "this study," because you have type 2 diabetes that is not controlled well with diet, exercise, and metformin treatment.

This consent form has information about this study so that you can decide if you want to participate. Ask the study doctor or study staff any questions about this study at any time. You can also talk to your family and friends about this study. Take as much time as you need to decide if you want to join this study.

The following section is a summary of information about this research study:

- This study is being done to see if the study drug called BI 456906 may help people with type 2 diabetes in the future.
- Your participation in this study is voluntary (your choice). You may choose to participate or may decide not to join this study. You can decide to participate now and change your mind later. Your decision will not affect your medical care or result in any penalty or loss of benefits to which you are entitled.
- This study is for research purposes only and will help to gain information for providing

better or new treatments for people in the future. This is different from regular medical care, where the purpose is to help each individual person.

- If you join this study, your type 2 diabetes may or may not improve. You may benefit from better control of your blood sugar (glucose), but no benefits can be promised. The results of this study may help other people with type 2 diabetes in the future.
- This study will involve study procedures such as: physical exams, electrocardiograms (ECGs), urine tests including urine drug screens, blood tests including genetic testing and infectious disease testing, completing diaries and questionnaires, suicide assessment interviews, self-monitoring of blood glucose (SMBG) at home, and fasting (nothing to eat or drink except water for 10 hours) before certain study visits and before most SMBG tests.
- If you are eligible to continue in this study, you will receive the drug being tested, BI 456906 or placebo, or a prescription drug called semaglutide (Ozempic®). A placebo looks like the study drug but has no drug in it. BI 456906, placebo, and semaglutide will be given by subcutaneous injection (an injection under the skin) either 1 time or 2 times a week.
- You will be in this study about 23 weeks and have about 13 visits to the study center. Two of the groups in this study will receive study drug injections 2 times a week. If you are assigned to 1 of those 2 groups, you will have about 20 visits to the study center.
- While taking part in this study, you may experience negative effects which may include possible side effects (risks) from the study procedures and the study drug or semaglutide. Refer to the sections below, “Description of the Study Procedures and their Possible Risks and Discomforts” and “What possible risks or discomforts can you expect from taking the study drug or semaglutide?,” for information about the possible side effects.
- During this study you will be asked to continue to take one of your usual medications (metformin) to treat your type 2 diabetes. For this study, this medication is called a background medication. The study doctor will tell you which, if any of your other medications you can continue to take during this study.
- Instead of taking part in this study, you may choose other treatment options that are listed in the section below, “What are your other choices if you do not join this study?”
- About 410 subjects (people who participate in a clinical research study) will take part in this study worldwide.

It is important that your personal doctor is aware that you are in a clinical research study because you may be taking an investigational study drug or semaglutide that could affect your health. With your permission, we will notify your personal doctor that you are taking part in this study.

This study is funded by the sponsor, Boehringer Ingelheim Pharmaceuticals, Inc. The study doctor and/or institution are being paid by the sponsor for the work done for this study. Any reference to the sponsor in this consent form also includes the sponsor’s research partners and

service providers (like clinical research organizations and laboratories) including companies belonging to the Boehringer Ingelheim Group of Companies.

What is the purpose of this study?

This study is being done to:

- Test different doses and different plans to slowly increase the dose of the study drug, BI 456906, given 1 or 2 times a week by an injection under the skin.
- Test the safety and side effects of BI 456906 compared to placebo.
- Test the effectiveness of BI 456906 compared to semaglutide in subjects with type 2 diabetes.
- Test how the study drug and semaglutide is used by the body, and how fast or slow the drugs move through or out of the body.
- Find the best starting dose and dose increase plan of BI 456906, and the best schedule (given 1 or 2 times a week) for future studies.

BI 456906 has not been approved by the U.S. Food and Drug Administration (FDA) as a treatment for any disease. Semaglutide (Ozempic®) has been approved by the FDA for treating adults with type 2 diabetes. The study drug and semaglutide are experimental for this study.

The drug, BI 456906, and the placebo being tested in this study will be referred to as "study drug" throughout this consent form.

What are your other choices if you do not join this study?

If you decide not to join this study, your other choices for treating type 2 diabetes are to:

- Stay on your current treatment;
- Take part in another clinical research study;
- Continue to stay on metformin;
- Receive semaglutide (Ozempic®), but not as part of a clinical study;
- Get other treatments; or
- Choose to receive no treatment.

Medications, such as Januvia®, Jardiance®, Glucotrol®, Tradjenta®, and Amaryl®, are available and approved for use in this country to treat adults with type 2 diabetes. There are other type 2 diabetes treatments that the study doctor can discuss with you.

The study doctor will discuss these options and their important potential risks and benefits with you before you decide whether you will take part in this study. You may also discuss your options with your regular doctor.

How will your information be protected if you join this study?

Your medical records and study-related medical records will be shared only as explained below and in the section included at the end of this consent form titled, "Authorization to Use and Share Your Protected Health Information" (Authorization).

During this study your data will be collected, which includes your personal identifiable information (any information that could identify you) and your Protected Health Information (PHI), which is medical information that identifies you, all information collected as part of this study, and the results from laboratory tests.

Reasonable safeguards will be put into place to protect the confidentiality of the data collected, but absolute confidentiality cannot be guaranteed. The data that directly identifies you are not included in any records nor used to label biological samples that are reviewed and/or copied or sent to the sponsor. Instead a unique code number is used. This is considered coded data.

The sponsor may share your data with scientists, medical researchers in other companies or academic institutions for the purpose of specific and approved scientific research. The sponsor may also use your data and/or share it with other investigators for future medical research beyond this study without your additional consent. The shared data will not include information that can identify you.

By having access, your past and current medical information, your study-related medical records, which may contain your name and any information that could identify you, and this consent and authorization form, may be reviewed and/or copied by the sponsor and any company that acquires the rights to the study drug (BI 456906) from the sponsor, Alpha IRB, the IRB overseeing this study, and regulatory authorities, such as the U.S. Food and Drug Administration (FDA) or similar agencies in other countries.

The sponsor of this clinical research study, Boehringer Ingelheim Pharmaceuticals, Inc., is the subsidiary of a parent company, Boehringer Ingelheim GmbH, which is located in Germany. Your data collected as part of this study may be sent to Germany and housed and processed on servers of its parent company in Germany.

What will happen if you join this study?

Before any study procedures are done, you will be asked to read this consent form. If you agree to join this study, you will be asked to sign and date this consent form.

This study includes a Screening Period, a Study Drug Period, an End of Treatment Visit, and a Follow-up Period. Each period or visit is explained in this consent form in the order that they will be completed.

The study procedures that will be done are listed in the following sections and the Visit Chart below. If you join this study, the study doctor or study staff will explain what happens at each study visit in more detail.

You will enter the Screening Period (Visit 1): Once you sign and date this consent form, certain procedures as listed in the Visit Chart below will be done to find out if you can continue in this study. You may need to come to the study center for more than one visit during this Screening Period.

You will need to inform the study doctor and/or study staff of all of your medical conditions, allergies, and any medications (prescribed or obtained over-the-counter) you may be taking. The study doctor will use this information, your medical history and the other screening procedures to see if you can continue in this study.

When a certain number of subjects have entered this study, no more subjects can be enrolled. If the screening procedures show that you can be in this study, the study doctor will let you know if you will be allowed to continue.

If the study doctor determines that you cannot continue in this study, you should not go to another study center to be screened again. If the study doctor determines you can continue in this study, you will enter the Study Drug Period.

You will enter the Study Drug Period: During this period, you will receive the study drug or semaglutide and have the study procedures as listed in the Visit Chart below.

BI 456906, placebo, and semaglutide will be given by subcutaneous injection (injection under the skin). You will be assigned by chance, like pulling a number out of a hat, to 1 of the 7 study drug groups listed below.

For Groups 1 to 6, each group will receive different doses. The dose will gradually increase up to Week 7 (except for one group). After Week 7 the dose will be the same for the remainder of this study.

- **Groups 1, 2, 3, and 4:** You will receive the study drug (BI 456906 or placebo) once a week. Doses will range from 0.3 mg to 2.7 mg per week.
- **Groups 5 and 6:** You will receive the study drug (BI 456906 or placebo) 2 times a week. Doses will range from 0.6 mg to 3.6 mg per week.

- **Group 7:** You will receive semaglutide once a week. The dose will gradually increase. You will receive 0.25 mg for the first 4 weeks, 0.5 mg for Weeks 5 to 8, and 1.0 mg for Weeks 9 to 16.

You will have about an 88% chance of being assigned to a group receiving study drug and about a 12% chance of being assigned to the group receiving semaglutide. If you are assigned to one of the groups receiving the study drug, you will have about an 86% chance of receiving the active study drug, BI 456906, and about a 14% chance of receiving placebo.

For Groups 1 to 6: No one (including you and the study staff) will know if you will be assigned to BI 456906 or the placebo. The study doctor will be able to find out if you are receiving BI 456906 or the placebo in case of an emergency. You will be told whether you will be taking the dose of the study drug 1 time or 2 times a week.

For Group 7: You will be told if you are assigned to semaglutide, and the dose you will be receiving.

For Visits 2 to 8:

For Groups 1 to 6: During each of your visits, you will receive the injections at the study center. From Visits 2 to 7, you will receive 1 or 2 injections into your abdomen (belly) while lying in a semi-upright position.

Starting at Visit 8, you will receive 2 injections each time the dose is given.

Each injection will take about 15 seconds. When you receive 2 injections, they will be given in different locations on the same side of your belly.

Additionally, for Groups 5 and 6: If you are assigned to Groups 5 or 6, since you will receive the study drug 2 times a week, the first weekly injection(s) will be given at the study center as indicated in the Visit Chart below. You will then return to the study center 3 to 4 days after each study visit to receive the second weekly injection dose. The study staff will let you know when to return for the second weekly dose.

For Group 7: Semaglutide will be given once a week at the study center using an injection pen. Injections may be given in the upper arms, thighs, or abdomen.

Between Visits 9 and 11:

You will be asked to take the injections at home between the study center visits (you will still receive the injections at the study center on days you have study visits). If you are assigned to Group 5 or 6, between Visits 11 and 12, you will also be asked to take the second weekly

injections at home.

If you do not want to take the injections at home, you can have the injections done at the study center by the study staff.

If you agree to take the injections at home, you will receive the following:

- Groups 1 to 6 will receive pre-filled syringes (injection devices that are already filled with your dose). You will take 2 injections in 2 different locations on the same side of your belly (either the right side or the left side). The next time you take your dose, you should use the other side of your belly.
- Group 7 will receive injection pens already filled with semaglutide. You will take 1 injection in your belly, thigh, or upper arm. A different injection site should be used each week when injecting the same part of the body.

You will receive training and an instruction sheet on how to give yourself the injections, as well as how to store the study drug or semaglutide.

If a dose is missed on the planned dosing day, and you are receiving injections once a week, you should take the dose as soon as possible, but no later than 2 days after the planned dosing time. If you are receiving injections twice a week, you should take a missed dose as soon as possible, but no later than 1 day after the planned dosing time. If more time has passed since the missed dose, then you should skip that dose and take the next planned dose.

The pre-filled syringes and injection pens have to be kept cool, so you will be given a cooler bag with frozen gel packs in which to carry them. You will need to bring the bags and frozen gel packs with you to the next study visit.

You will be given a diary to record the date and time you take the injections at home, where the dose was injected, and any reactions you may have at the injection site(s). You will bring the completed diary to your next study visit.

You will be given a special container (sharps container) that must be used to discard the used syringes and injection pens.

If you experience side effects from the study drug, at Visit 8 the dose may be decreased for certain dose groups.

If you experience side effects related to taking the study drug or semaglutide, or after receiving a reduced dose (if applicable), the study drug or semaglutide may be stopped.

If needed, the study doctor may prescribe medication(s) that may help relieve symptoms of

your diabetes, such as high blood sugar. The study doctor may also prescribe medication(s) to treat symptoms such as diarrhea, nausea, vomiting and stomach upset that you may have from taking the study drug or semaglutide. These medications are called rescue medications.

You will complete the End of Treatment (EOT) Visit: An EOT Visit will be done about 7 days after you stop taking the study drug or semaglutide.

When you stop the study drug or semaglutide, or decide to stop participating in this study, the study doctor will discuss your future treatment options.

You will enter the Follow-up (F/U) Period: For your safety, a F/U Visit will be done about 5 weeks after your last dose of the study drug or semaglutide. After your F/U Visit, you will have completed this study.

For your safety, any side effect(s) that continue after your last study visit will be followed by the study doctor until the side effect(s) resolve or are stable.

Optional Procedure: This study includes another study procedure that is an optional (your choice) part of this main study. The procedure includes the collection of blood samples for storage and potential future research testing.

You will be given a separate consent form with information so that you can decide whether or not you want to join this optional part. You do not have to join this optional part in order to participate in this main study.

Visit Chart: The procedures that will be done at each study visit are shown by the "X."

	Screening Period	**Study Drug Period**											**Follow -up**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 (EOT)**	**13**
Visit Week	**-2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**17**	**21**
Fasting (nothing to eat or drink except water for 10 hours)		X				X			X	X		X	X
Medical history, alcohol, drug, and licorice use	X												
Physical Examination and waist measurement	X	X					X					X	
Blood pressure, pulse, weight and ECG	X	X	X	X	X	X	X	X	X	X	X	X	X

	Screening Period	Study Drug Period											Follow-up
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12 (EOT)**	**13**
Visit Week	**-2**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**12**	**16**	**17**	**21**
Blood and urine tests (including genetic testing)[1]	X	X	X	X	X	X	X	X	X	X	X	X	X
Review questionnaires		X				X			X			X	
Receive study drug or semaglutide injection(s) at the study center[2]		X	X	X	X	X	X	X	X	X	X		
Receive training on giving yourself the injections									X	X	X[3]		
Self-monitoring of blood glucose (SMBG)	◄———	———	———	———	———	———	———	———	———	———	———	———	———►
Diet and exercise counseling		X		X		X			X	X	X	X	X
Receive supply of study drug or semaglutide									X	X	X[3]		
Bring diaries to the study center		X	X	X	X	X	X	X	X	X	X	X	X
Bring unused study drug or semaglutide to the study center										X	X	X	

[1] Refer to the "Blood and/or Urine Tests" section below for more information about the blood and urine tests that will be done.

[2] If you are assigned to Group 5 or 6, you will need to come back to the study center 3 to 4 days after Visits 2, 3, 4, 5, 6, 7 and 8 to receive a second injection of the study drug.

[3] At Visit 11, only Groups 5 and 6 will receive the supply of pre-filled syringes and receive training for the injections.

In addition to the study procedures listed above, the following will also be done:

- **Self-monitoring of blood glucose (SMBG) at Home:** You will be given an electronic self-monitoring blood glucose device to measure your blood glucose (sugar) levels at home. You will also be given instructions on how to use the device, and a diary to record your blood sugar levels. You will check and record your blood sugar levels as follows:
    - On 1 day during the Screening Period and again on 1 day between Visits 11 and 12, you will be asked to measure your blood sugar levels 7 times on the same day as

follows:

- Before each of your 3 meals
- 2 hours after each of your 3 meals
- At bedtime

- Visits 2 to 12: at least 1 time per week, after fasting (nothing to eat or drink except water for 10 hours)
- During the Follow-up Period: at least 1 time (after fasting)
- Any time you think you are having symptoms of high blood sugar or low blood sugar. The symptoms that you might feel are listed below:

Low Blood Sugar (hypoglycemia)

If your blood sugar (glucose) is low, you may have the following symptoms: sudden outbreaks of sweating, palpitations (irregular heartbeat), trembling, feeling of hunger, restlessness, pallor (pale skin), headaches, sleepiness, anxiety, uncertainty, problems with vision and speech, signs of paralysis (unable to move part of your body) and abnormal sensations (tingling, prickling or numbness anywhere on your body).

You should tell the study doctor if you notice any of these symptoms. In case you do have these symptoms, you should check your blood sugar using the device. If your blood sugar drops to less than 70 mg/dL you should contact the study doctor right away and follow the directions provided to you by the study doctor. If your blood sugar drops below 54 mg/dL, you should immediately eat or drink some carbohydrate (for example a glucose solution or fruit juice) and contact your study doctor. If the study doctor is not available and your symptoms do not improve seek immediate emergency medical care.

High Blood Sugar (hyperglycemia)

If your blood sugar is high, you may have the following symptoms: being more thirsty, dry mouth, and needing to urinate more often. Other signs include a loss of appetite, blurred vision, dizziness, stomach pain, nausea or vomiting, warm, dry or flushed skin, difficulty breathing, weakness, sleepiness, fruity smell on the breath and, in rare instances, coma.

If you have these symptoms or your blood sugar measurement is above 240 mg/dL, you should contact the study doctor right away.

- You will be asked to fast (have nothing to eat or drink but water) for 10 hours before the study Visits as listed in the Visit Chart above.
- You may be asked to come to the study center for additional unscheduled visits for testing if

the study doctor thinks it is necessary for your safety. The study staff may contact you to remind you about your study visit appointments and things you need to do for this study.

- At your study visits, the study doctor or study staff will ask you how you feel, and what medications you have taken since your last visit.
- At Visit 9, you will receive written instructions about how to give yourself the study drug or semaglutide injections at home, and how to store the drugs.

Description of the Study Procedures and their Possible Risks and Discomforts: The study procedures and their possible risks and discomforts are described below. There may be other risks which are not known or unforeseen at this time. Tell the study doctor or study staff if you have any symptoms or side effects from the study procedures at any time.

Except as indicated in this consent form, you may not be told the results from other tests and procedures done during this study.

- **Diaries:** You will be asked to complete 2 diaries as follows:
    - **SMBG Diary:** At Visit 1 you will receive a diary to record the blood sugar levels from the SMBG device (see "Self-monitoring of blood glucose (SMBG) at Home" section above) each time you use the device at home, and to record any symptoms of high or low blood sugar.
    - **Patient Dosing Diary:** If you give yourself the injections at home, you will record the date, time, and where you give yourself the injections, and any reactions you may have at the injection sites.

  You will bring your completed diaries to your next study visit to be reviewed by the study staff. The study staff will discuss this with you. You may find completing the diaries is tiring.

- **ECG (electrocardiogram):** This test measures the electrical activity of your heart. Sticky pads connected by wires to the ECG machine will be placed on your skin. The sticky pads may cause some redness or itching when the pads are removed.

- **Fasting:** Fasting (nothing to eat or drink except water for 10 hours) before certain study visits and/or before self-monitoring your blood glucose at home as listed above, may cause dizziness, headache, stomach discomfort, or fainting.

- **Subcutaneous Injection:** You will receive the study drug or semaglutide as an injection under the skin.

  You may feel mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site (where the needle is inserted). There is also a small risk of light-headedness

and/or fainting. In rare cases, the site where the needle is inserted can become infected or nerves may be damaged, and cause long-lasting abnormal sensations, damaged sensation of touch and lasting pain.

- **Interviews and Questionnaires:** You will be asked to answer questions by yourself as follows:

  Interviews will be done to assess:

  - **CSSR (Columbia-Suicide Severity Rating Scale):** You will be asked to answer questions to see if you have suicidal thoughts or behaviors. It will take about 5-10 minutes to complete.
  - If you have suicidal thoughts or behavior, the study doctor will advise you to see a psychiatrist.

  Questionnaires will be done to assess:

  - **Three Factor Eating Questionnaire**: You will answer questions about your eating behaviors.
  - **Patient Global Impression of Severity:** You will answer 1 question about how bad your diabetes is.
  - **Hunger Visual Analog:** This questionnaire is used to see how hungry you are.

  It will take about 5 to 8 minutes to complete the questionnaires.

  You may find the interviews and questionnaires are long, upsetting, or tiring. You may not like some of the questions or feel uncomfortable answering them. You can skip any question that makes you feel uncomfortable.

- **Blood and/or Urine Tests:** The purpose of these tests is described below. Blood will be taken with a needle from a vein in your arm. To take multiple blood samples, a small, thin, flexible tube (called an IV catheter) may be inserted into one of your veins using a needle (similar to a blood drawing needle).

  Before taking your blood, numbing medication may be applied to the skin to reduce the pain where the needle is inserted. You may have an allergic reaction to the numbing medication, which may make the skin red, itchy or swollen where the numbing medication was applied.

  - **Pregnancy Tests (for women who can become pregnant):** Your blood and/or urine will be tested to see if you are pregnant. The results must be negative in order for

you to continue in this study. You will be told if the pregnancy test results are positive.

- **Safety Tests:** Blood and urine will be taken to check your overall health and to check your disease status. If at any time during this study your blood tests show there may be a problem with your liver, you will be asked to return for additional tests to see why. These additional blood tests will check your liver function and for hepatitis.
- **Infectious Disease Tests:** Your blood will be tested at the Screening Visit to see if you have an infectious disease such as hepatitis (a disease that affects the liver) or HIV (human immunodeficiency virus) infection. You will be told the results of these tests.

  If you have an infectious disease such as, hepatitis or HIV infection, this information may have to be reported to a public health authority, depending on the state and local laws where this study is being done. If reported, your personal identifiable information such as your name, address, and phone number may also be reported.
- **Urine Drug Screen:** Your urine will be tested at the Screening Visit for narcotics and other street drugs.
- **Hb-A1c**: Your blood will be tested to measure an average of your blood sugar levels for the last 2 or 3 months.
- **Biomarker Tests:** Blood will be taken to see how the study drug or semaglutide works in your body and how your body responds to the study drug or semaglutide.
- **Anti-Drug Antibodies (ADA) and Neutralizing Antibodies (NAb) Tests:** Blood will be taken to measure your immune response to the study drug (when the body detects and defends itself against substances that appear unknown and/or harmful).
- **Pharmacokinetic (PK) Tests:** Blood will be taken to see how your body uses the study drug or semaglutide and how fast or slow the study drug or semaglutide moves through or out of your body.
- **Genetic Biomarker Testing:** Blood will be taken at Visit 2, or may be done at a later visit, to look at the DNA (deoxyribonucleic acid) in your cells to see if there are genes associated with diabetes and how the study drug or semaglutide work.

  Genes are a part of your DNA which determines things like the color of your hair or eyes. Your genes affect how you respond to drugs.

  Reports about any research using your sample for genetic testing and the results from the testing will <u>not</u> be given to you or the study doctor, any insurance company, your employer, your family, or any physician who treats you now or in the future. The results will not have any direct meaning for your health or your family members' health and will not affect your care. You will not receive any benefit from this testing.

Genetic testing may have additional risks with unauthorized access to your data. For example, if your genetic test information were shared with persons not permitted to see it, there is a possible risk you may be treated unfairly by employers, insurance providers or others. However, the chance that this information will be given to someone else who would use it against you is very small.

A federal law called the Genetic Information Non-discrimination Act (GINA) makes it illegal for health insurance companies, group health plans, and most employers to treat you differently based on your genetic information. However, this legal protection has limits (for example, it does not protect against discrimination (being treated unfairly) by companies selling life, disability or long-term care insurance) and it may not keep others from trying to treat you differently or unfairly.

If you do not want genetic testing to be done on your sample, you cannot participate in this study.

During or after a blood test, you may feel mild pain, local irritation, bleeding or bruising (a black and blue mark) at the puncture site (where the needle is inserted). There is also a small risk of light-headedness and/or fainting. In rare cases, the puncture site can become infected or nerves may be damaged, and cause long-lasting abnormal sensations, damaged sensation of touch and lasting pain. Frequent blood collection may cause anemia (low red blood cell count), which may create a need for blood transfusions.

The total amount of blood that will be taken for the whole study is about 37 tablespoons if you are assigned to Groups 1 to 6, and about 32 tablespoons if you are assigned to Group 7. If additional tests are needed, the amount of blood taken will be higher.

Will your samples be kept private?

Samples that may be sent to the study doctor's laboratory for analysis may be labeled with your name and other data about you. In general, only the study center and laboratory will have access to your data.

Samples that may be sent to a laboratory selected by the sponsor will be given a unique code number. This number is used in place of your name and other data about you to safeguard your confidentiality. In general, only the study center will have the link between your name and the code number.

However, sometimes another party, such as the sponsor or a regulatory agency, such as the U.S. Food and Drug Administration (FDA), may need to access your data to make sure this study is done in a safe and accurate manner.

The samples or parts of them may be transferred to the sponsor. The sponsor may also use your coded samples and/or share them with other investigators for future medical research beyond this study without your additional consent.

When will your samples be destroyed?

All samples collected for safety, Hb-A1c, pregnancy, infectious disease, and urine drug screen testing will be destroyed once the tests are completed or by the end of this study.

Any leftover blood samples from the genetic biomarker testing will be destroyed once testing is complete, but not later than 1 year after the end of the study and the sponsor completes a report that contains the study results.

Sample storage for additional research: The following samples will be stored for further research without your additional consent and will then be destroyed as indicated below.

- Your leftover blood taken for PK and ADA/NAb testing will be stored for additional testing to see how the drugs react over time. Testing may also be done to identify metabolites (products made by chemical reactions in your cells) from the PK samples. The samples will be destroyed once the additional testing is complete but not later than 5 years after the end of the study and the sponsor completes a report that contains the study results.
- Your leftover blood taken for biomarker testing will be stored for additional unknown biomarker testing and will be destroyed once the additional testing is complete but not later than 5 years after the end of the study and the sponsor completes a report that contains the study results.

The results of the future testing will be used for research purposes only and you or the study doctor will not be told the results, nor will the results be put in your health record. The results of the future testing will not have an effect on your care. You will not receive any benefit from this future testing.

If you do not want your samples to be stored for additional research, you cannot participate in this study.

What are your responsibilities if you join this study?

- You must tell the study doctor if you previously participated in this study or have been in another research study in the past year or are currently in another research study.
- While you are participating in this study, you should not take part in another study without approval from the study doctor.

- You may only participate in this study at this study center. You may harm yourself if you participate at multiple study centers.
- You will receive a Trial Identification Card to carry with you at all times. It is important that you tell other doctors about your participation in this study by showing this card.
- You must follow the instructions you are given by the study doctor and study staff. If you do not follow the instructions, your visit may have to be rescheduled.
- You should follow the recommended diet and exercise plan provided by the dietitian or study staff.
- Tell the study doctor or the study staff about all prescription and non-prescription medications or vaccines before you take them.
- At the Screening Visit you must tell the study doctor about any herbal products and dietary supplements that you are taking. You must not take dietary supplements and herbal products, such as St. John's wort, while you are in this study.
- Since you are taking metformin, tell the study doctor if you need a procedure that requires intravascular (by a vein) administration of iodine containing contrast agents as you must temporarily stop taking metformin at the time of or before the procedure until 48 hours after the procedure.
- Do not throw the study drug or semaglutide in the trash. The used syringes and injection pens must be put in the sharps container. Do not give your study drug or semaglutide to any other person to take and keep the study drug or semaglutide out of the reach of children and others who cannot read the label.
- You must store the study drug or semaglutide as indicated in the written instructions provided.
- You must remember to bring your unused study drug or semaglutide and all empty cartons from the used study drug or semaglutide to each of your study visits and explain if there is any lost or missing study drug or semaglutide. You will return the sharps container when it is full or at the end of the study.
- You should not donate blood while you are participating in the study and throughout the follow-up period.
- While you are in this study, you should avoid doing more physical activity than is normal for you, except to follow the exercise plan discussed with the dietitian or study staff.
- You will need to return the self-monitoring blood glucose device to the study center when your participation in this study is complete.
- Notify the study doctor or study staff if you move and provide your new address and contact information.

What if there is new information about this study?

As this study continues, the sponsor may learn more information about this study and/or the study drug. You will be notified of any changes to the study procedures, any newly discovered side effects, or any other new information about this study in a timely manner. This way you can decide if you want to continue to take part in this study. You may be asked to read a new consent form. If you agree to continue in this study, you will be asked to sign and date a new consent form.

What if you join this study and then change your mind about being in this study later?

If you join this study, you can stop the study drug or semaglutide or stop your participation at any time. Your decision to later withdraw from this study will not affect your medical care or result in any penalty or loss of benefits that you would have received.

If you decide to stop the study drug or semaglutide or withdraw from this study, it is important to tell the study doctor as soon as possible so the study drug or semaglutide can be stopped safely. There may be risks of stopping the study drug suddenly which the study doctor will discuss with you.

Listed below are two ways the study drug or semaglutide and/or your participation in this study may be stopped.

- **You may stop the study drug or semaglutide and participation completely whether or not you withdraw your consent:**

If you decide to stop taking the study drug or semaglutide and participation completely, you will be asked to complete the End of Treatment Visit and Follow-Up Visit procedures.

- **The study doctor may decide that you must stop the study drug or semaglutide or your participation:**

The study doctor may decide to stop the study drug or semaglutide or may take you out of this study without your consent, when in his/her judgment it is in your best health interest to do so. Some of the reasons why this may happen are listed below:

- If your type 2 diabetes is getting worse or does not improve and you need other treatment(s).
- Your metformin dose is changed more than 2 weeks in a row.
- If you (female subjects) become pregnant.
- If the study drug or semaglutide or procedures are found to be unsafe or ineffective.

- If you cannot take the study drug or semaglutide or participate as instructed.
- If this study is stopped by the sponsor or a regulatory agency.
- For unforeseen reasons that make it necessary to stop your participation in this study.

If you are removed from this study, the study doctor will explain why. The study doctor and study staff will discuss your future treatment options.

You have the right to withdraw your consent at any time. If you are removed from this study or if you withdraw your consent and decide to leave this study completely, all data and samples collected up to the time of your withdrawal, including data and samples gathered at any of your final assessments, will still be used to ensure the correct completion and documentation of this clinical research study and to comply with applicable laws. Once you withdraw your consent, you cannot continue to take part in this study.

If you leave this study early for any reason, a member of the study staff may contact you or someone you designate (for example, a family member or your family doctor) to collect follow-up information about your current health status. This information is necessary to preserve and interpret the data correctly.

What possible risks or discomforts can you expect from taking the study drug or semaglutide?

There are risks to taking part in any research study. If you only receive placebo, you will not receive an active treatment for your type 2 diabetes. Your type 2 diabetes may not improve, or it could get worse during the course of this study. However, you will be able to continue to take metformin for your type 2 diabetes.

If you receive active study drug or semaglutide, then side effects may occur. Some of those side effects can be treated. Some side effects may go away when you stop taking the study drug or semaglutide. Some side effects can be mild, but others may continue longer or become permanent. Some may be life-threatening or fatal (causing death).

As with any drug, an allergic reaction can occur. Allergic reactions can be mild or more serious and can even result in death. Common symptoms of an allergic reaction are rash, itching, skin problems, swelling of the face and throat, or breathing difficulties.

If you think you are having an allergic reaction, call the study doctor right away at the telephone number listed on page 1 of this consent form. If you are having trouble breathing or have an emergency, call 911 right away or go to the emergency room.

Taking the study drug or semaglutide may cause you to have one or more of the side effects (or adverse events [unwanted side effects]) listed below.

The study doctor or the study staff will go through the description of the known side effects with you. They are willing to discuss any questions you may have about the severity and frequency of risks and other potential discomforts. In addition to the side effects listed, there is always the risk of developing side effects which are not known at this time and which are not foreseeable.

You will be monitored to check for these risks. The study drug or semaglutide may be stopped if any signs of drug toxicity (harmful side effects) or other damage occurs.

You need to tell the study doctor or the study staff immediately if you experience any side effects.

The currently known side effects or discomforts of BI 456906 include:

Currently, BI 456906 has only been tested in subjects with obesity. In those clinical studies, specific side effects, as listed below, were observed after subjects received several doses of the study drug. Such effects occurred more often with higher doses.

Very common: More than 10% risk that this will happen:

- Decreased appetite
- Early satiety (feeling full after eating a small amount of food)
- Stomach ache (dyspepsia)
- Feeling sick to your stomach (nausea)
- Frequent, loose or liquid bowel movements (diarrhea)
- Vomiting
- Abdominal distention (air [gas] in the belly)
- Belching (eructation)
- Inflammation of the nose and throat (nasopharyngitis)
- Irregular heartbeats

Common (between 1% and 10% risk that this will happen):

- Belly pain
- Constipation (decreased bowel movement)
- Burning sensation in the throat or chest
- Complete or partial blockage of the electrical signals that pass between the upper and lower chambers of the heart
- Fast heart beat
- Extra heartbeats
- Tiredness

The currently known side effects or discomforts of semaglutide include:

Very common: More than 10% risk that this will happen:

- Feeling sick to your stomach

Common (between 1% and 10% risk that this will happen):

- Vomiting
- Frequent, loose or liquid bowel movements
- Belly pain
- Constipation

Unknown:

- Cancer of the thyroid gland
- Inflammation of the pancreas (pancreatitis)
- Kidney failure
- Disease of the retina (back part of your eye) caused by diabetes (diabetic retinopathy)
- Hypersensitivity (allergic type reaction)

An antidote, a treatment to counter-act the effects of BI 456906 or semaglutide is not available. If you have side effects or adverse events from the study drug or semaglutide, they will have to be treated as symptoms occur.

Background Medication (metformin):

The study doctor will discuss with you the risks of the metformin which you will continue to take during this study.

Rescue Medications:

The study doctor will discuss with you the risks and benefits of the rescue medications which you may be prescribed during your participation in this study.

Information about Birth Control and Pregnancy:

As with any study drug (BI 456906), as well as semaglutide, the effect of these drugs on the unborn child is unknown and unforeseeable.

For Female Subjects:

If you decide to take part in this study and you are able to become pregnant, you must be willing to have a pregnancy test done before you take the study drug or semaglutide, regularly at study visits and at the end of this study. Further, you must avoid becoming pregnant while

you take part in this study.

There may be risks that are not known and unforeseeable at this time that may occur to you or your unborn child if pregnancy occurs.

You cannot participate in this study if you are pregnant, breastfeeding or plan to become pregnant during your study participation. You must use 2 medically acceptable methods of birth control throughout the study and for at least 5 weeks after the last dose of the study drug or semaglutide.

You must use one highly effective non-barrier method and your partner must use one barrier method (condom) or be vasectomized (with appropriate post-vasectomy documentation of the absence of sperm in the ejaculate and provided your partner is the sole sexual partner).

Oral contraceptives (birth control pills) are not permitted. Your study doctor will talk to you about the best methods of birth control for you.

Highly effective non-barrier methods for this study include:

- Hormonal methods of birth control that prevent ovulation:
  - Combined estrogen-progestogen contraception: intravaginal (vaginal ring) or transdermal (patch)
  - Progestogen-only contraception: injectable or implantable
- Placement of intrauterine device (IUD) or intrauterine hormone releasing system (IUS)
- Bilateral tubal occlusion (tubes surgically blocked or tied)

Or, you may choose complete sexual abstinence from male-female sex. If you choose abstinence (not to have sex) as your method of birth control, you must completely avoid having vaginal sex with a male partner.

Abstinence is defined as being in line with your preferred and usual lifestyle. Periodic abstinence, for example, calendar, ovulation, symptothermal (signs of ovulation), post-ovulation methods; declaring abstinence while taking the study drug or semaglutide, and withdrawal are not acceptable.

You do not need to use birth control to be in this study if you are not able to get pregnant due to being postmenopausal (1 year without your period without another medical cause) or have had one of the following, both ovaries removed, a hysterectomy (removal of the uterus), or both fallopian tubes removed.

If you are pregnant or think you could be pregnant, it is important that you tell the study doctor or study staff immediately. If you become pregnant during this study, you will stop the study drug or semaglutide. You will be asked to complete the End of Treatment Visit and Follow-Up Visit procedures. Your health and your baby's health will be monitored throughout your

pregnancy. Even if you are no longer in this study, the study doctor will contact you after your baby is born to find out about the baby's health.

For Male Subjects:

There may be risks that are not known and unforeseeable at this time that may occur to your unborn child if your female partner becomes pregnant.

Because the study drug or semaglutide may affect an unborn child, you should not father a child while taking part in this study.

If you are able to father a child and your female partner(s) is able to become pregnant, you will be required to use a condom or you must be vasectomized (with appropriate post-vasectomy documentation of absence of sperm in the ejaculate). In addition, your female partner(s) must use a highly effective method of birth control such as indicated in the list above for female subjects and including oral contraceptives (birth control pills), or you may choose complete sexual abstinence from male-female sex. Your study doctor will talk to you about the best methods of birth control for you.

If you choose abstinence (not to have sex) as your method of birth control, you must completely avoid having vaginal sex with your female partner(s). Abstinence is defined as being in line with your preferred and usual lifestyle. Periodic abstinence, for example, calendar, ovulation, symptothermal (signs of ovulation), post-ovulation methods; declaring abstinence while taking the study drug or semaglutide, and withdrawal are not acceptable.

The above methods of birth control must be used beginning at Screening, during this study and for at least 5 weeks after the last dose of the study drug or semaglutide.

You should tell your female partner(s) that you are participating in this study.

Tell the study doctor or study staff right away if your female partner becomes pregnant during your participation in this study. You will be asked to provide your partner's contact information. Even if you are no longer in this study, your partner will be asked to read and sign a consent form if she agrees to give permission for the study doctor to collect information about her pregnancy, the outcome (delivery) of the birth of your baby, and about your baby's health after birth. The study doctor needs to report this to the sponsor.

Will it cost you anything to be in this study?

All study procedures including lab work, tests, study visits, the study drug or semaglutide, and the use of the SMBG device during this study, are provided to you at no cost by the sponsor and will not be billed to you or your insurance company as long as you are in this study.

Either you or your insurance company will be billed for the cost of procedures, your metformin, and any medications that you need for any standard medical care of your type 2 diabetes (including high blood sugar), and you will be responsible for the payment of any copayment, coinsurance or deductible required by your insurance company.

Will you get paid for joining this study?

For your travel and inconvenience related to your participation, you will be paid for the study visits you complete according to the following schedule: $50.00 each for Visits 1 through 13.

If you do not complete this study, for any reason, you will be paid for the study visits you do complete.

If you come to the study center for any unscheduled visits, you will be paid $50.00 for each additional visit.

Depending on your travel distance to and from the study center, you may be reimbursed for lodging, meals, and your own car mileage or transportation. The study staff will discuss this with you.

This will be paid to you at each completed study visit.

In connection with this study, you will only receive the payments specified above.

If you receive $600.00 or more in study payments in a calendar year, this will be reported to the Internal Revenue Service (IRS) and you will receive a Form 1099-MISC. You will need to provide your Social Security number for this purpose.

If you have any questions regarding costs or payment for participation, contact the study doctor at the telephone number listed on page 1 of this consent form.

The sponsor will be the owner of the study results. If commercial products or other valuable discoveries result from research using your samples and/or data, these products and discoveries may be owned, patented, licensed, or otherwise developed for commercial sale by the sponsor, other researchers, or companies. If this should occur, you will not receive any payment or have any ownership or rights from any discoveries that may result from such research.

What happens if you are injured during this study?

If you are injured or become ill as a result of your participation in this study, contact the study doctor who will provide you with, or arrange for, the reasonably necessary medical care. The costs of treatment for an injury or illness that you suffer during this study may be covered by the study sponsor, the institution, or billed to you or your insurer just like other medical costs, depending on a number of factors.

If you have a government health plan, if you have a non-government health plan that does not cover the medical costs of your injury or illness, or if you are uninsured, the sponsor will pay for medical treatment of any illness or injury that directly results from the use of the study drug or semaglutide, or the study procedures as indicated in this consent form. You must follow the directions of the study doctor to be eligible for this coverage. Except as just set forth, there are no plans to pay for injuries related to your medical condition(s) or injuries related to expected complications from those conditions.

The sponsor does not have a program to provide any other payment or compensation to you, including for lost wages or mental distress. You do not lose any of your legal rights by signing and dating this form.

Any payments made by the sponsor as outlined above require the sponsor to determine if you are covered by Medicare and, if so, to report certain information to Medicare. To do so, the sponsor will need certain personal identifiable information from you, including your name, date of birth, Medicare/Medicaid health insurance claim number, and Social Security number. The sponsor agrees to use this information only for Medicare reporting purposes and those outlined in the Authorization to Use and Share Your Protected Health Information section, which is included at the end of this consent form.

Will information about this study be available on any Web sites?

Clinical Study Web sites and Publication

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

The results of this study will be published on Boehringer Ingelheim's Trial Web site (http://trials.boehringer-ingelheim.com). The results may also appear in other clinical trial registries in countries in which this study is conducted. The results will not include information that can identify you.

The results of this study may also be published in a professional journal or presented at scientific meetings. Your identity will not be shared in those presentations.

What if you have questions about this study?

If you have questions, concerns or complaints about this study, contact the study doctor at the telephone number listed on page 1 of this form.

If you have questions, concerns or complaints about your rights as a research volunteer or about taking part in this study, or to obtain information or offer input, you may contact Marianne Thornton, toll free at (888) 265-5766 between the hours of 8:00am-5:00pm Pacific Time.

Alpha Independent Review Board
1001 Avenida Pico, Suite C #497
San Clemente, CA 92673
(888) 265-5766 (toll free)

Alpha IRB is a group of people who perform independent review of research studies to protect the rights and welfare of study participants. Although Alpha IRB has approved the information provided in this informed consent form and has approved for the study doctor to do the study, this does not mean the Alpha IRB has approved you being in the study, or that the study is without risks. You must consider the information in this consent form for yourself and decide if you want to be in this study.

Study Subject Number: _____

Declaration of Informed Consent

What should you do if you want to join this study?

If you want to join this study, you have to sign and date this consent form **and** the Authorization to Use and Share Your Protected Health Information section below. You will be given a copy of this signed and dated consent form.

By signing and dating this consent form **and** the Authorization to Use and Share Your Protected Health Information section below, you are saying:

- I have read each page of this consent form and all my questions have been answered.
- I was given enough time to decide whether to participate.
- I agree to the collection, storage, processing, transfer and use of my data as explained in the above information.
- I agree the samples and sample-related data, collected during this study, no longer belong to me.
- I agree to return the Self-monitoring Blood Glucose device when my participation in this study ends.
- I authorize (give permission for) the release of my medical records to the sponsor, representatives of the sponsor, the U.S. Food and Drug Administration (FDA), the Department of Health and Human Services (DHHS), regulatory agencies similar to the FDA and DHHS in other countries, and Alpha IRB.
- I voluntarily consent to participate in this study, and I understand that I may withdraw my consent at any time as described in this consent form.
- I do not give up any of my legal rights by signing and dating this form.

_____

Subject's First and Last Name (Print)

_____

Subject's Signature Date

Statement of Study Doctor or Study Personnel:

I certify that I have explained to the above individual(s) the nature and purpose, the possible benefits and possible risks associated with participation in this study. I have answered any questions that have been raised.

I acknowledge my responsibility for the care and well-being of the subject, to respect the rights and wishes of the subject, and to conduct this study according to Good Clinical Practices and regulations.

_____

Study Doctor or Study Personnel First and Last Name (Print)

_____

Study Doctor or Study Personnel Signature Date

Study Personnel Providing an Additional Explanation:

Note to Site: In addition to the above Study Doctor or Study Personnel signature, if another study staff member provides further explanation about this study, that study staff member must also sign and date this consent form.

_____

Study Personnel First and Last Name (Print)

_____

Study Personnel Signature Date

*Proceed to read, sign, and date the "**Authorization to Use and Share Your Protected Health Information**" form below*

Authorization to Use and Share Your Protected Health Information

The study doctor and his/her study staff (who together will be referred to as the “study doctor”) will need to use and share your Protected Health Information (PHI) in order to conduct this study. PHI is medical information that identifies you because it includes information, such as your name, address, Social Security number, medical record number and/or other details about you.

Your PHI will include all information used to see if you qualify for this study and information collected from the study procedures. This may include, but is not limited to, the following types of medical information:

- Your medical history including all medical records from the study center and your other health care providers and other sensitive information including treatment for or history of HIV/AIDS, hepatitis, substance abuse and/or alcoholism, mental health diagnoses and treatment.
- Physical exams, results from laboratory tests, infectious disease testing, drug screens, genetic testing, ECGs, self-monitoring blood sugar tests, and information from questionnaires, interviews, and diaries.
- Your response to the study drug or semaglutide and information related to study visits and phone calls.
- Other tests or procedures that may be performed and not listed.

If you give your permission by signing and dating this form, the study doctor may:

- Use and share your PHI with the sponsor. Any reference to the sponsor includes the sponsor’s research partners and service providers (like clinical research organizations and laboratories), including companies belonging to the Boehringer Ingelheim Group of Companies, and any person or company that acquires the rights to the study drug (BI 456906) from the sponsor.

  The service providers could also include vendors hired by the sponsor to assist in the coordination of your participation in this study (for example, by providing appointment message reminders, debit cards, devices to use during your participation in this study, to review public records, etc.).

- Give some of your identifying information (for example, the last four digits of your Social Security number and/or your initials or a few letters of your last name) to the sponsor to confirm you have not previously enrolled in this study and to protect the integrity of this study.
- Give your PHI to the sponsor for use as necessary to comply with the section of this consent form entitled, “What happens if you are injured during this study?”
- Share your PHI with Alpha IRB, the IRB overseeing this study and regulatory authorities such as the U.S. Food and Drug Administration (FDA) or similar regulators in other countries.
- Request and use your Social Security number, along with your name and date of birth for IRS tax reporting requirements if you receive study payments of $600 or more in a calendar year.

Your name and any information that directly identifies you are not included in any records nor used to label samples the study doctor sends to the sponsor. Instead, a unique code number is used. The study doctor can link (match) the code to your records or samples in order to identify you and will provide your identity to the sponsor if it is necessary to do so as described above (for example, if a government agency requires the sponsor to contact you). The link will remain at the study center for a maximum of 30 years and the link will then be destroyed by the study doctor. After that it is not possible to link your unique code number directly back to you.

Your coded samples and/or coded data may be transferred within the United States or to other countries for analysis. The sponsor will ensure that those who analyze your samples and data on behalf of the sponsor in other countries have appropriate measures to provide an adequate level of protection.

The study doctor will keep your original identifiable medical records from this study. By having access to these records, this consent form and authorization form may be reviewed and/or copied by the sponsor, the IRB overseeing this study, and regulatory authorities, such as the U.S. Food and Drug Administration (FDA) or similar regulators in other countries. The sponsor and these entities may use this information to understand the disease/condition from this study, the study and the study results;

determine the safety and effectiveness of the study drug; check that this study was run properly; determine whether to approve the study drug; and improve the quality of this study and other clinical research studies. The sponsor and/or the study doctor may communicate information to doctors at other institutions participating in this study. Once your PHI has been given to a third party, including the sponsor, federal privacy laws may no longer protect it from further disclosure.

With this authorization, the sponsor may conduct further medical research beyond this study. Your coded data from this study can be combined and analyzed with data from other studies. The purpose is to learn more about your disease and other diseases, different responses to treatments and new treatment options to improve quality and efficiency in the drug development process. The additional use of your coded data will not be part of another clinical study.

This authorization does not have an expiration date. Permission to use and share your PHI will continue until it is no longer needed by the sponsor or the study doctor. However, in California and any other state that requires an expiration date, the Authorization will expire 50 years after you sign and date this authorization form.

You have the right to see and copy any of the PHI gathered about you, but not until this study is complete. Your right to access, inspect and/or amend the PHI will be suspended until this study is complete to protect the scientific integrity of this study. You will be given access to your PHI as soon as reasonably possible.

You also have the right to withdraw this permission at any time by telling or by providing a written request to the study doctor. When you withdraw your permission, (1) you will not be able to continue in this study; (2) the study doctor will stop collecting new data about you; and (3) the study doctor may still use and share your PHI that was collected before your withdrawal if that information is necessary to make sure the rest of this study is carried out appropriately. For example, the study doctor may need to include in the study records and to report to the sponsor information about your vital (health) status in the study doctor’s possession at the time you revoke (cancel) your authorization or search public records to see if you are alive

or deceased at the time this study is completed. The sponsor or any other entity authorized to receive information under this authorization form may continue using any PHI that it received from the study doctor before your withdrawal of permission.

By signing and dating this authorization form, you are giving your permission for the study doctor to use and give out your PHI as described in this authorization. If you do not give your permission, you will not be able to join this study. You will be given a copy of this signed and dated form.

Acknowledgement of Authorization

_____

Subject's First and Last Name (Print)

_____

Subject's Signature Date