EXHIBIT 21

REDACTED IN ITS ENTIRETY

EXHIBIT 22

REDACTED IN ITS ENTIRETY

EXHIBIT 23

REDACTED IN ITS ENTIRETY

EXHIBIT 24

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OGIVRI safely and effectively. See full prescribing information for OGIVRI.

OGIVRI (trastuzumab-dkst) for injection, for intravenous use
Initial U.S. Approval: 2017

OGIVRI (trastuzumab-dkst) is biosimilar* to HERCEPTIN (trastuzumab).

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

See full prescribing information for complete boxed warning

Cardiomyopathy: trastuzumab products can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue Ogivri for cardiomyopathy. (2.3, 5.1)

Infusion Reactions, Pulmonary Toxicity: Discontinue Ogivri for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome. (5.2, 5.4)

Embryo-Fetal Toxicity: Exposure to trastuzumab products during pregnancy can result in oligohydramnios, in some cases complicated by pulmonary hypoplasia and neonatal death. Advise patients of these risks and the need for effective contraception. (5.3, 8.1, 8.3)

INDICATIONS AND USAGE

Ogivri is a HER2/neu receptor antagonist indicated for:

- The treatment of HER2-overexpressing breast cancer. (1.1, 1.2)
- The treatment of HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma. (1.3)

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product (1, 2.1).

DOSAGE AND ADMINISTRATION

For intravenous (IV) infusion only. Do not administer as an IV push or bolus. (2.2)

Do not substitute Ogivri (trastuzumab-dkst) for or with ado-trastuzumab emtansine. (2.2)

Perform HER2 testing using FDA-approved tests by laboratories with demonstrated proficiency. (1, 2.1)

Adjuvant Treatment of HER2-Overexpressing Breast Cancer (2.2)

Administer at either:

- Initial dose of 4 mg/kg over 90 minute IV infusion, then 2 mg/kg over 30 minute IV infusion weekly for 12 weeks (with paclitaxel or docetaxel) or 18 weeks (with docetaxel/carboplatin). One week after the last weekly dose of Ogivri, administer 6 mg/kg as an IV infusion over 30 to 90 minutes every three weeks to complete a total of 52 weeks of therapy, or
- Initial dose of 8 mg/kg over 90 minutes IV infusion, then 6 mg/kg over 30 to 90 minutes IV infusion every three weeks for 52 weeks.

Metastatic HER2-Overexpressing Breast Cancer (2.2)

- Initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent weekly doses of 2 mg/kg as 30 minute IV infusions.

Metastatic HER2-Overexpressing Gastric Cancer (2.2)

- Initial dose of 8 mg/kg over 90 minutes IV infusion, followed by 6 mg/kg over 30 to 90 minutes IV infusion every 3 weeks.

DOSAGE FORMS AND STRENGTHS

- For Injection: 420 mg lyophilized powder in a multiple-dose vial for reconstitution

CONTRAINDICATIONS

- None (4)

WARNINGS AND PRECAUTIONS

- Exacerbation of Chemotherapy-Induced Neutropenia. (5.5, 6.1)

ADVERSE REACTIONS

Adjuvant Breast Cancer

- Most common adverse reactions (≥ 5%) are headache, diarrhea, nausea, and chills. (6.1)

Metastatic Breast Cancer

- Most common adverse reactions (≥ 10%) are fever, chills, headache, infection, congestive heart failure, insomnia, cough, and rash. (6 1)

Metastatic Gastric Cancer

- Most common adverse reactions (≥ 10%) are neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Mylan Pharmaceuticals Inc. at 1-877-446-3679 (1-877-4-INFO-RX) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Females and Males of Reproductive Potential: Verify the pregnancy status of females prior to initiation of Ogivri (8.3).

See 17 for PATIENT COUNSELING INFORMATION.

*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of Ogivri has been demonstrated for the condition(s) of use (e.g. indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: 12/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: CARDIOMYOPATHY, INFUSION REACTIONS, EMBRYO-FETAL TOXICITY, and PULMONARY TOXICITY

Cardiomyopathy
Administration of trastuzumab products can result in sub-clinical and clinical cardiac failure. The incidence and severity was highest in patients receiving trastuzumab with anthracycline-containing chemotherapy regimens.

Evaluate left ventricular function in all patients prior to and during treatment with Ogivri. Discontinue Ogivri treatment in patients receiving adjuvant therapy and withhold Ogivri in patients with metastatic disease for clinically significant decrease in left ventricular function *[see Dosage and Administration (2.3) and Warnings and Precautions (5.1)]*.

Infusion Reactions; Pulmonary Toxicity
Administration of trastuzumab products can result in serious and fatal infusion reactions and pulmonary toxicity. Symptoms usually occur during or within 24 hours of administration. Interrupt Ogivri infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue Ogivri for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome *[see Warnings and Precautions (5.2, 5.4)]*.

Embryo-Fetal Toxicity
Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception *[see Warnings and Precautions (5.3) and Use in Specific Populations (8.1, 8.3)]*.

1 INDICATIONS AND USAGE

1.1 Adjuvant Breast Cancer

Ogivri is indicated for adjuvant treatment of HER2 overexpressing node positive or node negative (ER/PR negative or with one high risk feature *[see Clinical Studies (14.1)]*) breast cancer

- as part of a treatment regimen consisting of doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel
- as part of a treatment regimen with docetaxel and carboplatin
- as a single agent following multi-modality anthracycline based therapy.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product *[see Dosage and Administration (2.1)]*.

1.2 Metastatic Breast Cancer

Ogivri is indicated:

- In combination with paclitaxel for first-line treatment of HER2-overexpressing metastatic breast cancer
- As a single agent for treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product*[see Dosage and Administration (2.1)]*.

1.3 Metastatic Gastric Cancer

Ogivri is indicated, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma who have not received prior treatment for metastatic disease.

Select patients for therapy based on an FDA-approved companion diagnostic for a trastuzumab product *[see Dosage and Administration (2.1)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Patient Selection

Select patients based on HER2 protein overexpression or HER2 gene amplification in tumor specimens *[see Indications and Usage (1) and Clinical Studies (14)]*. Assessment of HER2 protein overexpression and HER2 gene amplification should be performed using FDA-approved tests specific for breast or gastric cancers by laboratories with demonstrated proficiency. Information on the FDA-approved tests for the detection of HER2 protein overexpression and HER2 gene amplification is available at: http://www.fda.gov/CompanionDiagnostics.

Assessment of HER2 protein overexpression and HER2 gene amplification in metastatic gastric cancer should be performed using FDA-approved tests specifically for gastric cancers due to differences in gastric vs. breast histopathology, including incomplete membrane staining and more frequent heterogeneous expression of HER2 seen in gastric cancers.

Improper assay performance, including use of suboptimally fixed tissue, failure to utilize specified reagents, deviation from specific assay instructions, and failure to include appropriate controls for assay validation, can lead to unreliable results.

2.2 Recommended Doses and Schedules

- **Do not administer as an intravenous push or bolus. Do not mix Ogivri with other drugs.**
- **Do not substitute Ogivri (trastuzumab-dkst) for or with ado-trastuzumab emtansine.**

Adjuvant Treatment, Breast Cancer:
Administer according to one of the following doses and schedules for a total of 52 weeks of Ogivri therapy:
During and following paclitaxel, docetaxel, or docetaxel/carboplatin:

- Initial dose of 4 mg/kg as an intravenous infusion over 90 minutes then at 2 mg/kg as an intravenous infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin).
- One week following the last weekly dose of Ogivri, administer Ogivri at 6 mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks.

As a single agent within three weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:

- Initial dose at 8 mg/kg as an intravenous infusion over 90 minutes

- Subsequent doses at 6 mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks *[see Dosage and Administration (2.3)]*.
- Extending adjuvant treatment beyond one year is not recommended *[see Adverse Reactions (6.1)]*.

Metastatic Treatment, Breast Cancer:

- Administer Ogivri, alone or in combination with paclitaxel, at an initial dose of 4 mg/kg as a 90-minute intravenous infusion followed by subsequent once weekly doses of 2 mg/kg as 30-minute intravenous infusions until disease progression.

Metastatic Gastric Cancer:

- Administer Ogivri at an initial dose of 8 mg/kg as a 90 minute intravenous infusion followed by subsequent doses of 6 mg/kg as an intravenous infusion over 30 to 90 minutes every three weeks until disease progression *[see Dosage and Administration (2.3)]*.

2.3 Important Dosing Considerations

If the patient has missed a dose of Ogivri by one week or less, then the usual maintenance dose (weekly schedule: 2 mg/kg; three-weekly schedule: 6 mg/kg) should be administered as soon as possible. Do not wait until the next planned cycle. Subsequent Ogivri maintenance doses should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

If the patient has missed a dose of Ogivri by more than one week, a re-loading dose of Ogivri should be administered over approximately 90 minutes (weekly schedule: 4 mg/kg; three-weekly schedule: 8 mg/kg) as soon as possible. Subsequent Ogivri maintenance doses (weekly schedule: 2 mg/kg; three-weekly schedule 6 mg/kg) should be administered 7 days or 21 days later according to the weekly or three-weekly schedules, respectively.

Infusion Reactions

[see Boxed Warning, Warnings and Precautions (5.2)]

- Decrease the rate of infusion for mild or moderate infusion reactions
- Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Discontinue Ogivri for severe or life-threatening infusion reactions.

Cardiomyopathy

[see Boxed Warning, Warnings and Precautions (5.1)]

Assess left ventricular ejection fraction (LVEF) prior to initiation of Ogivri and at regular intervals during treatment. Withhold Ogivri dosing for at least 4 weeks for either of the following:

- ≥16% absolute decrease in LVEF from pre-treatment values
- LVEF below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values.

Ogivri may be resumed if, within 4 to 8 weeks, the LVEF returns to normal limits and the absolute decrease from baseline is ≤15%.

Permanently discontinue Ogivri for a persistent (>8 weeks) LVEF decline or for suspension of Ogivri dosing on more than 3 occasions for cardiomyopathy.

2.4 Preparation for Administration

To prevent medication errors, it is important to check the vial labels to ensure that the drug being prepared and administered is Ogivri (trastuzumab-dkst) and not ado-trastuzumab emtansine.

420 mg Multiple-dose vial

Reconstitution: Reconstitute each 420 mg vial of Ogivri with 20 mL of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative to yield a multiple-dose solution containing 21 mg/mL trastuzumab-dkst that delivers 20 mL (420 mg trastuzumab-dkst). In patients with known hypersensitivity to benzyl alcohol, reconstitute with 20 mL of Sterile Water for Injection (SWFI) without preservative to yield a single use solution.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject the 20 mL of diluent into the vial containing the lyophilized cake of Ogivri. The stream of diluent should be directed into the lyophilized cake. The reconstituted vial yields a solution for multiple-dose use, containing 21 mg/mL trastuzumab-dkst.
- Swirl the vial gently to aid reconstitution. **DO NOT SHAKE.**
- Slight foaming of the product may be present upon reconstitution. Allow the vial to stand undisturbed for approximately 5 minutes.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Inspect visually for particulates and discoloration. The solution should be free of visible particulates, clear to slightly opalescent and colorless to pale yellow.
- Store reconstituted Ogivri in the refrigerator at 2° to 8°C (36° to 46°F), discard unused Ogivri after 28 days. If Ogivri is reconstituted with SWFI without preservative, use immediately and discard any unused portion. **Do not freeze.**

Dilution:

- Determine the dose (mg) of Ogivri *[see Dosage and Administration (2.1)]*. Calculate the volume of the 21 mg/mL reconstituted Ogivri solution needed, withdraw this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP. **DO NOT USE DEXTROSE (5%) SOLUTION.**
- Gently invert the bag to mix the solution.
- The solution of Ogivri for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Chloride Injection, USP, should be stored at 2° to 8°C (36° to 46°F) for no more than 24 hours prior to use. **Do not freeze.**

3 DOSAGE FORMS AND STRENGTHS

For injection: 420 mg of Ogivri as an off-white to pale yellow, preservative-free lyophilized powder in a multiple-dose vial.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Cardiomyopathy

Trastuzumab products can cause left ventricular cardiac dysfunction, arrhythmias, hypertension, disabling cardiac failure, cardiomyopathy, and cardiac death *[see Boxed Warning: Cardiomyopathy]*. Trastuzumab products can also cause asymptomatic decline in left ventricular ejection fraction (LVEF).

There is a 4 to 6 fold increase in the incidence of symptomatic myocardial dysfunction among patients receiving trastuzumab products as a single agent or in combination therapy compared with those not receiving trastuzumab products. The highest absolute incidence occurs when a trastuzumab product is administered with an anthracycline.

Withhold Ogivri for ≥ 16% absolute decrease in LVEF from pre-treatment values or an LVEF value below institutional limits of normal and ≥ 10% absolute decrease in LVEF from pretreatment values *[see Dosage and Administration (2.3)]*. The safety of continuation or resumption of Ogivri in patients with trastuzumab product-induced left ventricular cardiac dysfunction has not been studied.

Patients who receive anthracycline after stopping Ogivri may also be at increased risk of cardiac dysfunction *[see Drug Interactions (7) and Clinical Pharmacology (12.3)]*.

Cardiac Monitoring: Conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:

- Baseline LVEF measurement immediately prior to initiation of Ogivri
- LVEF measurements every 3 months during and upon completion of Ogivri
- Repeat LVEF measurement at 4 week intervals if Ogivri is withheld for significant left ventricular cardiac dysfunction *[see Dosage and Administration (2.3)]*
- LVEF measurements every 6 months for at least 2 years following completion of Ogivri as a component of adjuvant therapy.

In Study 1, 15% (158/1031) of patients discontinued trastuzumab due to clinical evidence of myocardial dysfunction or significant decline in LVEF after a median follow-up duration of 8.7 years in the AC-TH arm. In Study 3 (one-year trastuzumab treatment), the number of patients who discontinued trastuzumab due to cardiac toxicity at 12.6 months median duration of follow-up was 2.6% (44/1678). In Study 4, a total of 2.9% (31/1056) of patients in the TCH arm (1.5% during the chemotherapy phase and 1.4% during the monotherapy phase) and 5.7% (61/1068) of patients in the AC-TH arm (1.5% during the chemotherapy phase and 4.2% during the monotherapy phase) discontinued trastuzumab due to cardiac toxicity.

Among 64 patients receiving adjuvant chemotherapy (Studies 1 and 2) who developed congestive heart failure, one patient died of cardiomyopathy, one patient died suddenly without documented etiology and 33 patients were receiving cardiac medication at last follow-up. Approximately 24% of the surviving patients had recovery to a normal LVEF (defined as ≥ 50%) and no symptoms on continuing medical management at the time of last follow-up. Incidence of congestive heart

failure is presented in Table 1. The safety of continuation or resumption of Ogivri in patients with trastuzumab product-induced left ventricular cardiac dysfunction has not been studied.

Table 1
Incidence of Congestive Heart Failure in Adjuvant Breast Cancer Studies

		Incidence of CHF	
Study	Regimen	Trastuzumab	Control
1 & 2[a]	AC[b] → Paclitaxel + Trastuzumab	3.2% (64/2000)[c]	1.3% (21/1655)
3[d]	Chemo →Trastuzumab	2% (30/1678)	0.3% (5/1708)
4	AC[b] → Docetaxel + Trastuzumab	2% (20/1068)	0.3% (3/1050)
4	Docetaxel + Carbo + Trastuzumab	0.4% (4/1056)	0.3% (3/1050)

[a] Median follow-up duration for studies 1 and 2 combined was 8.3 years in the AC → TH arm.
[b] Anthracycline (doxorubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy and 1 patient with sudden death without documented etiology.
[d] Includes NYHA II-IV and cardiac death at 12.6 months median duration of follow-up in the one-year trastuzumab arm.

In Study 3 (one-year trastuzumab treatment), at a median follow-up duration of 8 years, the incidence of severe CHF (NYHA III & IV) was 0.8%, and the rate of mild symptomatic and asymptomatic left ventricular dysfunction was 4.6%.

Table 2
Incidence of Cardiac Dysfunction[a] in Metastatic Breast Cancer Studies

		Incidence			
		NYHA I–IV		NYHA III–IV	
Study	Event	Trastuzumab	Control	Trastuzumab	Control
5 (AC)[b]	Cardiac Dysfunction	28%	7%	19%	3%
5 (paclitaxel)	Cardiac Dysfunction	11%	1%	4%	1%
6	Cardiac Dysfunction[c]	7%	N/A	5%	N/A

[a] Congestive heart failure or significant asymptomatic decrease in LVEF.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[c] Includes 1 patient with fatal cardiomyopathy.

In Study 4, the incidence of NCI-CTC Grade 3/4 cardiac ischemia/infarction was higher in the trastuzumab containing regimens (AC-TH: 0.3% (3/1068) and TCH: 0.2% (2/1056)) as compared to none in AC-T.

5.2 Infusion Reactions

Infusion reactions consist of a symptom complex characterized by fever and chills, and on occasion included nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asthenia *[see Adverse Reactions (6.1)]*.

In post-marketing reports, serious and fatal infusion reactions have been reported. Severe reactions, which include bronchospasm, anaphylaxis, angioedema, hypoxia, and severe hypotension, were usually reported during or immediately following the initial infusion. However, the onset and clinical course were variable, including progressive worsening, initial improvement followed by clinical deterioration, or delayed post-infusion events with rapid clinical deterioration. For fatal events, death occurred within hours to days following a serious infusion reaction.

Interrupt Ogivri infusion in all patients experiencing dyspnea, clinically significant hypotension, and intervention of medical therapy administered (which may include epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen). Patients should be evaluated and carefully monitored until complete resolution of signs and symptoms. Permanent discontinuation should be strongly considered in all patients with severe infusion reactions.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated with trastuzumab products after experiencing a severe infusion reaction. Prior to resumption of trastuzumab infusion, the majority of patients who experienced a severe infusion reaction were pre-medicated with antihistamines and/or corticosteroids. While some patients tolerated trastuzumab infusions, others had recurrent severe infusion reactions despite pre-medications.

5.3 Embryo-Fetal Toxicity

Trastuzumab products can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death.

Verify the pregnancy status of females of reproductive potential prior to the initiation of Ogivri. Advise pregnant women and females of reproductive potential that exposure to Ogivri during pregnancy or within 7 months prior to conception can result in fetal harm. Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Ogivri [see Use in Specific Populations (8.1, 8.3) and Clinical Pharmacology (12.3)].

5.4 Pulmonary Toxicity

Trastuzumab product use can result in serious and fatal pulmonary toxicity. Pulmonary toxicity includes dyspnea, interstitial pneumonitis, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, pulmonary insufficiency and hypoxia, acute respiratory distress syndrome, and pulmonary fibrosis. Such events can occur as sequelae of infusion reactions *[see Warnings and Precautions (5.2)]*. Patients with symptomatic intrinsic lung disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, appear to have more severe toxicity.

5.5 Exacerbation of Chemotherapy-Induced Neutropenia

In randomized, controlled clinical trials, the per-patient incidences of NCI-CTC Grade 3 to 4 neutropenia and of febrile neutropenia were higher in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to those who received chemotherapy alone. The incidence of septic death was similar among patients who received trastuzumab and those who did not *[see Adverse Reactions (6.1)]*.

6 ADVERSE REACTIONS

The following adverse reactions are discussed in greater detail in other sections of the label:

- Cardiomyopathy *[see Warnings and Precautions (5.1)]*
- Infusion Reactions *[see Warnings and Precautions (5.2)]*
- Embryo-Fetal Toxicity *[see Warnings and Precautions (5.3)]*
- Pulmonary Toxicity *[see Warnings and Precautions (5.4)]*
- Exacerbation of Chemotherapy-induced Neutropenia *[see Warnings and Precautions (5.5)]*

The most common adverse reactions in patients receiving trastuzumab products in the adjuvant and metastatic breast cancer setting are fever, nausea, vomiting, infusion reactions, diarrhea, infections, increased cough, headache, fatigue, dyspnea, rash, neutropenia, anemia, and myalgia. Adverse reactions requiring interruption or discontinuation of trastuzumab product treatment include CHF, significant decline in left ventricular cardiac function, severe infusion reactions, and pulmonary toxicity *[see Dosage and Administration (2.3)]*.

In the metastatic gastric cancer setting, the most common adverse reactions (≥ 10%) that were increased (≥ 5% difference) in patients receiving trastuzumab products as compared to patients receiving chemotherapy alone were neutropenia, diarrhea, fatigue, anemia, stomatitis, weight loss, upper respiratory tract infections, fever, thrombocytopenia, mucosal inflammation, nasopharyngitis, and dysgeusia. The most common adverse reactions which resulted in discontinuation of trastuzumab product treatment in the absence of disease progression were infection, diarrhea, and febrile neutropenia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Adjuvant Breast Cancer Studies

The data below reflect exposure to one-year trastuzumab therapy across three randomized, open-label studies, Studies 1, 2, and 3, with (n = 3678) or without (n = 3363) trastuzumab in the adjuvant treatment of breast cancer.

The data summarized in Table 3 below, from Study 3, reflect exposure to trastuzumab in 1678 patients; the median treatment duration was 51 weeks and median number of infusions was 18. Among the 3386 patients enrolled in the observation and one-year trastuzumab arms of Study 3 at a median duration of follow-up of 12.6 months in the trastuzumab arm, the median age was 49 years (range: 21 to 80 years), 83% of patients were Caucasian, and 13% were Asian.

Table 3
Adverse Reactions for Study 3[a], All Grades[b]

Adverse Reaction	One year Trastuzumab (n = 1678)	Observation (n = 1708)
Cardiac		
Hypertension	64 (4%)	35 (2%)
Dizziness	60 (4%)	29 (2%)
Ejection Fraction Decreased	58 (3.5%)	11 (0.6%)
Palpitations	48 (3%)	12 (0.7%)
Cardiac Arrhythmias[c]	40 (3%)	17 (1%)
Cardiac Failure Congestive	30 (2%)	5 (0.3%)
Cardiac Failure	9 (0.5%)	4 (0.2%)
Cardiac Disorder	5 (0.3%)	0 (0%)
Ventricular Dysfunction	4 (0.2%)	0 (0%)
Respiratory Thoracic Mediastinal Disorders		
Cough	81 (5%)	34 (2%)
Influenza	70 (4%)	9 (0.5%)
Dyspnea	57 (3%)	26 (2%)
URI	46 (3%)	20 (1%)
Rhinitis	36 (2%)	6 (0.4%)
Pharyngolaryngeal Pain	32 (2%)	8 (0.5%)
Sinusitis	26 (2%)	5 (0.3%)
Epistaxis	25 (2%)	1 (0.06%)
Pulmonary Hypertension	4 (0.2%)	0 (0%)
Interstitial Pneumonitis	4 (0.2%)	0 (0%)
Gastrointestinal Disorders		
Diarrhea	123 (7%)	16 (1%)
Nausea	108 (6%)	19 (1%)
Vomiting	58 (3.5%)	10 (0.6%)
Constipation	33 (2%)	17 (1%)
Dyspepsia	30 (2%)	9 (0.5%)
Upper Abdominal Pain	29 (2%)	15 (1%)
Musculoskeletal & Connective Tissue Disorders		
Arthralgia	137 (8%)	98 (6%)
Back Pain	91 (5%)	58 (3%)
Myalgia	63 (4%)	17 (1%)
Bone Pain	49 (3%)	26 (2%)
Muscle Spasm	46 (3%)	3 (0.2%)
Nervous System Disorders		

Headache	162 (10%)	49 (3%)
Paraesthesia	29 (2%)	11 (0.6%)
Skin & Subcutaneous Tissue Disorders		
Rash	70 (4%)	10 (0.6%)
Nail Disorders	43 (2%)	0 (0%)
Pruritus	40 (2%)	10 (0.6%)
General Disorders		
Pyrexia	100 (6%)	6 (0.4%)
Edema Peripheral	79 (5%)	37 (2%)
Chills	85 (5%)	0 (0%)
Asthenia	75 (4.5%)	30 (2%)
Influenza-like Illness	40 (2%)	3 (0.2%)
Sudden Death	1 (0.06%)	0 (0%)
Infections		
Nasopharyngitis	135 (8%)	
UTI	39 (3%)	
Immune System Disorders		
Hypersensitivity	10 (0.6%)	1 (0.06%)
Autoimmune Thyroiditis	4 (0.3%)	0 (0%)

[a] Median follow-up duration of 12.6 months in the one-year trastuzumab treatment arm.
[b] The incidence of Grade 3 or higher adverse reactions was < 1% in both arms for each listed term.
[c] Higher level grouping term.

In Study 3, a comparison of 3-weekly trastuzumab treatment for two years versus one year was also performed. The rate of asymptomatic cardiac dysfunction was increased in the 2-year trastuzumab treatment arm (8.1% versus 4.6% in the one-year trastuzumab treatment arm). More patients experienced at least one adverse reaction of Grade 3 or higher in the 2-year trastuzumab treatment arm (20.4%) compared with the one-year trastuzumab treatment arm (16.3%).

The safety data from Studies 1 and 2 were obtained from 3655 patients, of whom 2000 received trastuzumab; the median treatment duration was 51 weeks. The median age was 49 years (range: 24 to 80); 84% of patients were White, 7% Black, 4% Hispanic, and 3% Asian.

In Study 1, only Grade 3 to 5 adverse events, treatment-related Grade 2 events, and Grade 2–5 dyspnea were collected during and for up to 3 months following protocol-specified treatment. The following non-cardiac adverse reactions of Grade 2 to 5 occurred at an incidence of at least 2% greater among patients receiving trastuzumab plus chemotherapy as compared to chemotherapy alone: fatigue (29.5% vs. 22.4%), infection (24.0% vs. 12.8%), hot flashes (17.1% vs. 15.0%), anemia (12.3% vs. 6.7%), dyspnea (11.8% vs. 4.6%), rash/desquamation (10.9% vs. 7.6%), leukopenia (10 5% vs 8.4%), neutropenia (6.4% vs. 4.3%), headache (6.2% vs. 3.8%), pain (5.5% vs. 3.0%), edema (4.7% vs. 2.7%) and insomnia (4.3% vs. 1.5%). The majority of these events were Grade 2 in severity.

In Study 2, data collection was limited to the following investigator-attributed treatment-related adverse reactions: NCI-CTC Grade 4 and 5 hematologic toxicities, Grade 3 to 5 non-hematologic toxicities, selected Grade 2 to 5 toxicities associated with taxanes (myalgia, arthralgias, nail changes, motor neuropathy, sensory neuropathy) and Grade 1 to 5 cardiac toxicities occurring during chemotherapy and/or trastuzumab treatment. The following non-cardiac adverse reactions of Grade 2 to 5 occurred at an incidence of at least 2% greater among patients receiving trastuzumab plus chemotherapy as compared to chemotherapy alone: arthralgia (12.2% vs. 9.1%), nail changes (11.5% vs.6.8%), dyspnea (2.4% vs. 0.2%), and diarrhea (2.2% vs. 0%). The majority of these events were Grade 2 in severity.

Safety data from Study 4 reflect exposure to trastuzumab as part of an adjuvant treatment regimen from 2124 patients receiving at least one dose of study treatment [AC-TH: n = 1068; TCH: n = 1056]. The overall median treatment duration was 54 weeks in both the AC-TH and TCH arms. The median number of infusions was 26 in the AC-TH arm and 30 in the TCH arm, including weekly infusions during the chemotherapy phase and every three week dosing in the monotherapy period. Among these patients, the median age was 49 years (range 22 to 74 years). In Study 4, the toxicity profile was similar to that reported in Studies 1, 2, and 3 with the exception of a low incidence of CHF in the TCH arm.

Metastatic Breast Cancer Studies

The data below reflect exposure to trastuzumab in one randomized, open-label study, Study 5, of chemotherapy with (n = 235) or without (n = 234) trastuzumab in patients with metastatic breast cancer, and one single-arm study (Study 6; n = 222) in patients with metastatic breast cancer. Data in Table 4 are based on Studies 5 and 6.

Among the 464 patients treated in Study 5, the median age was 52 years (range: 25 to 77 years). Eighty-nine percent were White, 5% Black, 1% Asian and 5% other racial/ethnic groups. All patients received 4 mg/kg initial dose of trastuzumab followed by 2 mg/kg weekly. The percentages of patients who received trastuzumab treatment for ≥6 months and ≥12 months were 58% and 9%, respectively.

Among the 352 patients treated in single agent studies (213 patients from Study 6), the median age was 50 years (range 28 to 86 years), 86% were White, 3% were Black, 3% were Asian, and 8% in other racial/ethnic groups. Most of the patients received 4 mg/kg initial dose of trastuzumab followed by 2 mg/kg weekly. The percentages of patients who received trastuzumab treatment for ≥6 months and ≥12 months were 31% and 16%, respectively.

Table 4

Per-Patient Incidence of Adverse Reactions Occurring in ≥5% of Patients in Uncontrolled Studies or at Increased Incidence in the Trastuzumab Arm (Studies 5 and 6)

	Single Agent[a] n = 352	Trastuzumab + Paclitaxel n = 91	Paclitaxel Alone n = 95	Trastuzumab + AC[b] n = 143	AC[b] Alone n = 135
Body as a Whole					

Pain	47%	61%	62%	57%	42%
Asthenia	42%	62%	57%	54%	55%
Fever	36%	49%	23%	56%	34%
Chills	32%	41%	4%	35%	11%
Headache	26%	36%	28%	44%	31%
Abdominal pain	22%	34%	22%	23%	18%
Back pain	22%	34%	30%	27%	15%
Infection	20%	47%	27%	47%	31%
Flu syndrome	10%	12%	5%	12%	6%
Accidental injury	6%	13%	3%	9%	4%
Allergic reaction	3%	8%	2%	4%	2%
Cardiovascular					
Tachycardia	5%	12%	4%	10%	5%
Congestive heart failure	7%	11%	1%	28%	7%
Digestive					
Nausea	33%	51%	9%	76%	77%
Diarrhea	25%	45%	29%	45%	26%
Vomiting	23%	37%	28%	53%	49%
Nausea and vomiting	8%	14%	11%	18%	9%
Anorexia	14%	24%	16%	31%	26%
Heme & Lymphatic					
Anemia	4%	14%	9%	36%	26%
Leukopenia	3%	24%	17%	52%	34%
Metabolic					
Peripheral edema	10%	22%	20%	20%	17%
Edema	8%	10%	8%	11%	5%
Musculoskeletal					
Bone pain	7%	24%	18%	7%	7%
Arthralgia	6%	37%	21%	8%	9%
Nervous					
Insomnia	14%	25%	13%	29%	15%
Dizziness	13%	22%	24%	24%	18%
Paresthesia	9%	48%	39%	17%	11%
Depression	6%	12%	13%	20%	12%
Peripheral neuritis	2%	23%	16%	2%	2%
Neuropathy	1%	13%	5%	4%	4%
Respiratory					
Cough increased	26%	41%	22%	43%	29%
Dyspnea	22%	27%	26%	42%	25%
Rhinitis	14%	22%	5%	22%	16%
Pharyngitis	12%	22%	14%	30%	18%
Sinusitis	9%	21%	7%	13%	6%
Skin					

Rash	18%	38%	18%	27%	17%
Herpes simplex	2%	12%	3%	7%	9%
Acne	2%	11%	3%	3%	< 1%
Urogenital					
Urinary tract infection	5%	18%	14%	13%	7%

[a] Data for Trastuzumab single agent were from 4 studies, including 213 patients from Study 6.
[b] Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.

Metastatic Gastric Cancer

The data below are based on the exposure of 294 patients to trastuzumab in combination with a fluoropyrimidine (capecitabine or 5-FU) and cisplatin (Study 7). In the trastuzumab plus chemotherapy arm, the initial dose of trastuzumab 8 mg/kg was administered on Day 1 (prior to chemotherapy) followed by 6 mg/kg every 21 days until disease progression. Cisplatin was administered at 80 mg/m^2 on Day 1 and the fluoropyrimidine was administered as either capecitabine 1000 mg/m^2 orally twice a day on Days 1 to14 or 5-fluorouracil 800 mg/m^2/day as a continuous intravenous infusion Days 1 through 5. Chemotherapy was administered for six 21 day cycles. Median duration of trastuzumab treatment was 21 weeks; median number of trastuzumab infusions administered was eight.

Table 5
Study 7: Per Patient Incidence of Adverse Reactions of All Grades
(Incidence ≥ 5% between Arms) or Grade 3/4 (Incidence > 1 % between Arms)
and Higher Incidence in Trastuzumab Arm

	Trastuzumab + FC (N = 294) N (%)		FC (N = 290) N (%)	
Body System/Adverse Event	All Grades	Grades 3/4	All Grades	Grades 3/4
Investigations				
Neutropenia	230 (78)	101 (34)	212 (73)	83 (29)
Hypokalemia	83 (28)	28 (10)	69 (24)	16 (6)
Anemia	81 (28)	36 (12)	61 (21)	30 (10)
Thrombocytopenia	47 (16)	14 (5)	33 (11)	8 (3)
Blood and Lymphatic System Disorders				
Febrile Neutropenia	—	15 (5)	—	8 (3)
Gastrointestinal Disorders				
Diarrhea	109 (37)	27 (9)	80 (28)	11 (4)
Stomatitis	72 (24)	2 (1)	43 (15)	6 (2)
Dysphagia	19 (6)	7 (2)	10 (3)	1 (≤ 1)
Body as a Whole				
Fatigue	102 (35)	12 (4)	82 (28)	7 (2)
Fever	54 (18)	3 (1)	36 (12)	0 (0)
Mucosal Inflammation	37 (13)	6 (2)	18 (6)	2 (1)

Chills	23 (8)	1 (≤ 1)	0 (0)	0 (0)
Metabolism and Nutrition Disorders				
Weight Decrease	69 (23)	6 (2)	40 (14)	7 (2)
Infections and Infestations				
Upper Respiratory Tract Infections	56 (19)	0 (0)	29 (10)	0 (0)
Nasopharyngitis	37 (13)	0 (0)	17 (6)	0 (0)
Renal and Urinary Disorders				
Renal Failure and Impairment	53 (18)	8 (3)	42 (15)	5 (2)
Nervous System Disorders				
Dysgeusia	28 (10)	0 (0)	14 (5)	0 (0)

The following subsections provide additional detail regarding adverse reactions observed in clinical trials of adjuvant breast cancer, metastatic breast cancer, metastatic gastric cancer, or post-marketing experience.

Cardiomyopathy
Serial measurement of cardiac function (LVEF) was obtained in clinical trials in the adjuvant treatment of breast cancer. In Study 3, the median duration of follow-up was 12.6 months (12.4 months in the observation arm; 12.6 months in the 1-year trastuzumab arm); and in Studies 1 and 2, 7.9 years in the AC-T arm, 8.3 years in the AC-TH arm. In Studies 1 and 2, 6% of all randomized patients with post-AC LVEF evaluation were not permitted to initiate trastuzumab following completion of AC chemotherapy due to cardiac dysfunction (LVEF < LLN or ≥ 16 point decline in LVEF from baseline to end of AC). Following initiation of trastuzumab therapy, the incidence of new-onset dose-limiting myocardial dysfunction was higher among patients receiving trastuzumab and paclitaxel as compared to those receiving paclitaxel alone in Studies 1 and 2, and in patients receiving one-year trastuzumab monotherapy compared to observation in Study 3 (see Table 6, Figures 1 and 2). The per-patient incidence of new-onset cardiac dysfunction, as measured by LVEF, remained similar when compared to the analysis performed at a median follow-up of 2.0 years in the AC-TH arm. This analysis also showed evidence of reversibility of left ventricular dysfunction, with 64.5% of patients who experienced symptomatic CHF in the AC-TH group being asymptomatic at latest follow-up, and 90.3% having full or partial LVEF recovery.

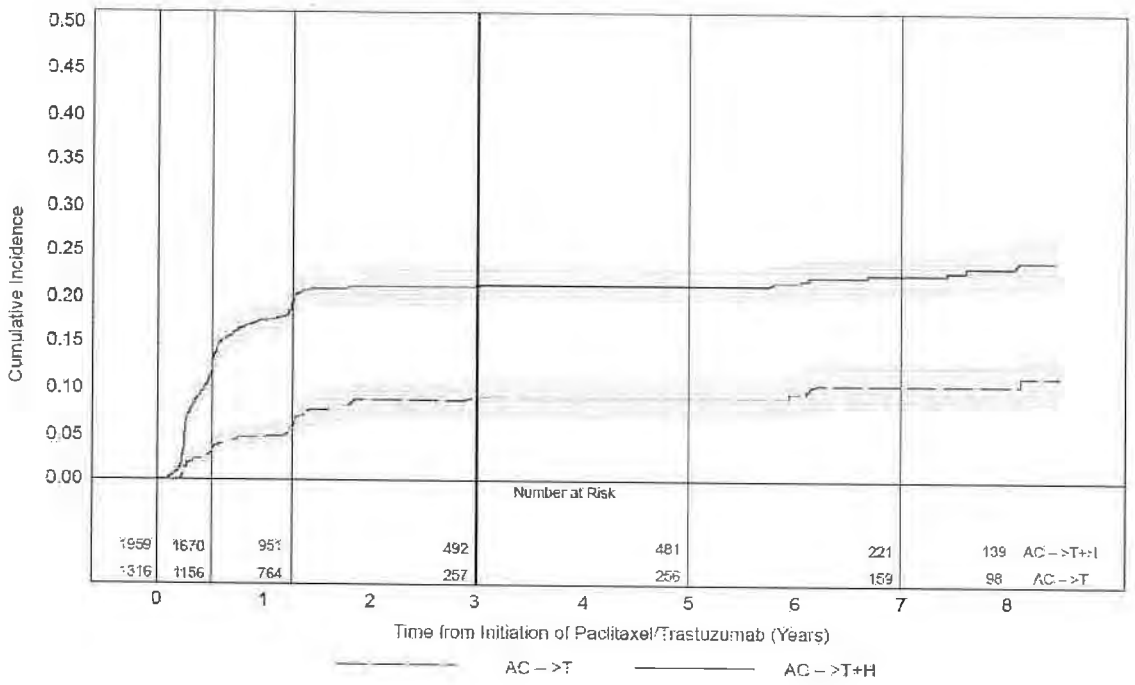
Table 6[a]
Per-patient Incidence of New Onset
Myocardial Dysfunction (by LVEF) Studies 1, 2, 3 and 4

	LVEF <50% and Absolute Decrease from Baseline			Absolute LVEF Decrease	
	LVEF < 50%	≥ 10% decrease	≥ 16% decrease	< 20% and ≥ 10%	≥ 20%
Studies 1 & 2[b,c]					

AC → TH (n = 1856)	23.1% (428)	18.5% (344)	11.2% (208)	37.9% (703)	8.9% (166)
AC → T (n = 1170)	11.7% (137)	7.0% (82)	3.0% (35)	22.1% (259)	3.4% (40)
Study 3[d]					
Trastuzumab (n = 1678)	8.6% (144)	7.0% (118)	3.8% (64)	22.4% (376)	3.5% (59)
Observation (n = 1708)	2.7% (46)	2.0% (35)	1.2% (20)	11.9% (204)	1.2% (21)
Study 4[e]					
TCH (n = 1056)	8.5% (90)	5.9% (62)	3.3% (35)	34.5% (364)	6.3% (67)
AC → TH (n = 1068)	17% (182)	13.3% (142)	9.8% (105)	44.3% (473)	13.2% (141)
AC → T (n = 1050)	9.5% (100)	6.6% (69)	3.3% (35)	34% (357)	5.5% (58)

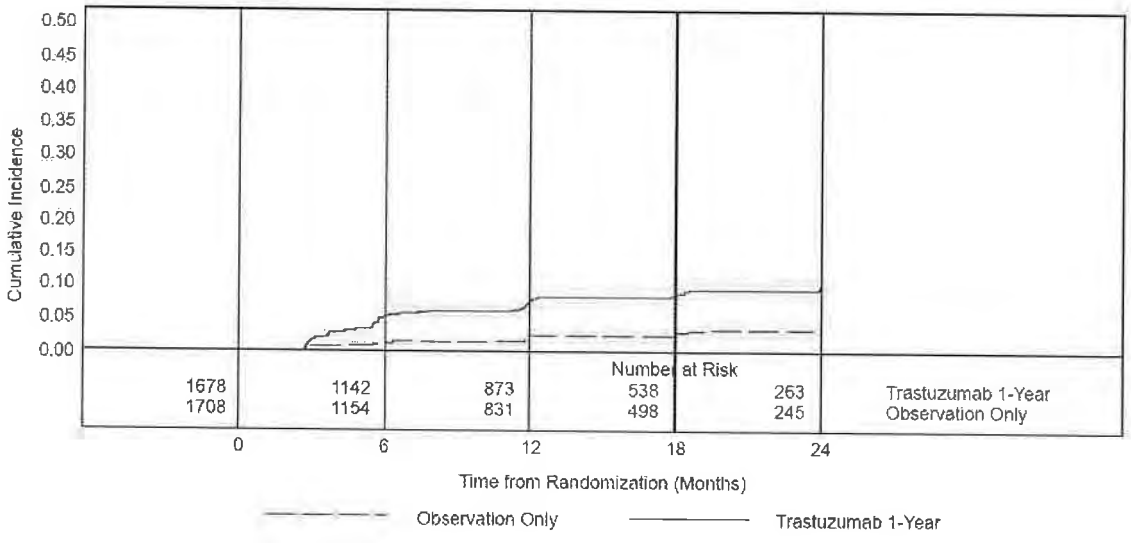
[a] For Studies 1, 2 and 3, events are counted from the beginning of trastuzumab treatment. For Study 4, events are counted from the date of randomization.
[b] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC → T) or paclitaxel plus trastuzumab (AC → TH).
[c] Median duration of follow-up for Studies 1 and 2 combined was 8.3 years in the AC → TH arm.
[d] Median follow-up duration of 12.6 months in the one-year trastuzumab treatment arm.
[e] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC → T) or docetaxel plus trastuzumab (AC → TH); docetaxel and carboplatin plus trastuzumab (TCH).

Figure 1
Studies 1 and 2: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



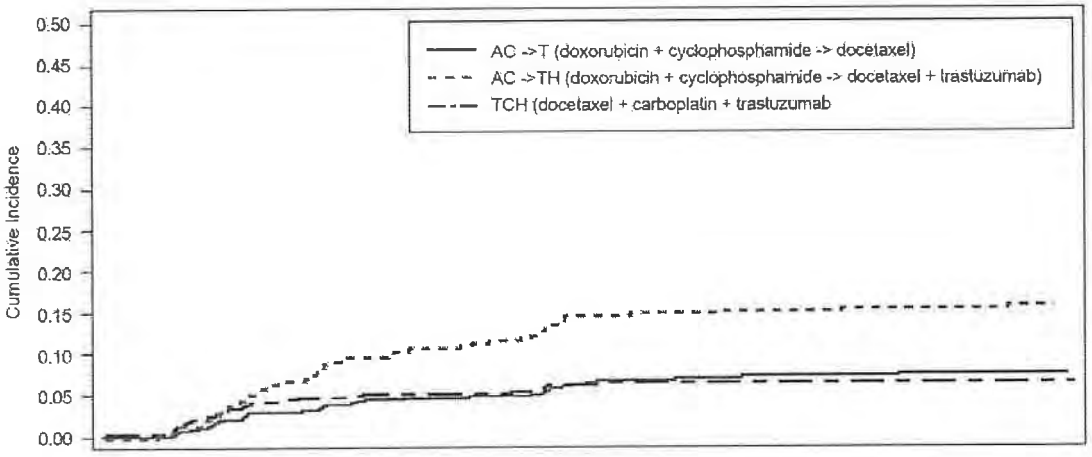
Time 0 is initiation of paclitaxel or trastuzumab + paclitaxel therapy.

Figure 2
Study 3: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Time 0 is the date of randomization

Figure 3
Study 4: Cumulative Incidence of Time to First LVEF Decline of ≥ 10 Percentage Points from Baseline and to Below 50% with Death as a Competing Risk Event



Number at Risk						
AC->T	1050	947	836	523	359	259
AC->TH	1068	975	839	474	315	248
TCH	1056	975	877	535	350	271

Time 0 is the date of randomization.

The incidence of treatment emergent congestive heart failure among patients in the metastatic breast cancer trials was classified for severity using the New York Heart Association classification system (I–IV, where IV is the most severe level of cardiac failure) (see Table 2). In the metastatic breast cancer trials, the probability of cardiac dysfunction was highest in patients who received trastuzumab concurrently with anthracyclines.

In Study 7, 5.0% of patients in the trastuzumab plus chemotherapy arm compared to 1.1% of patients in the chemotherapy alone arm had LVEF value below 50% with a ≥ 10% absolute decrease in LVEF from pretreatment values.

Infusion Reactions
During the first infusion with trastuzumab, the symptoms most commonly reported were chills and fever, occurring in approximately 40% of patients in clinical trials. Symptoms were treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of trastuzumab infusion); permanent discontinuation of trastuzumab for infusion reactions was required in < 1% of patients. Other signs and/or symptoms may include nausea, vomiting, pain (in some cases at tumor sites), rigors, headache, dizziness, dyspnea, hypotension, elevated blood pressure, rash, and asthenia. Infusion reactions occurred in 21% and 35% of patients, and were severe in 1.4% and 9% of patients, on second or subsequent trastuzumab infusions administered as monotherapy or in combination with chemotherapy, respectively. In the post-marketing setting,

severe infusion reactions, including hypersensitivity, anaphylaxis, and angioedema have been reported.

Anemia
In randomized controlled clinical trials, the overall incidence of anemia (30% vs. 21% [Study 5]), of selected NCI-CTC Grade 2 to 5 anemia (12.3% vs. 6.7% [Study 1]), and of anemia requiring transfusions (0.1% vs. 0 patients [Study 2]) were increased in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone. Following the administration of trastuzumab as a single agent (Study 6), the incidence of NCI-CTC Grade 3 anemia was < 1%. In Study 7 (metastatic gastric cancer), on the trastuzumab containing arm as compared to the chemotherapy alone arm, the overall incidence of anemia was 28% compared to 21% and of NCI-CTC Grade 3/4 anemia was 12.2% compared to 10.3%.

Neutropenia
In randomized controlled clinical trials in the adjuvant setting, the incidence of selected NCI-CTC Grade 4 to 5 neutropenia (1.7% vs. 0.8% [Study 2]) and of selected Grade 2 to 5 neutropenia (6.4% vs. 4.3% [Study 1]) were increased in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone. In a randomized, controlled trial in patients with metastatic breast cancer, the incidences of NCI-CTC Grade 3/4 neutropenia (32% vs. 22%) and of febrile neutropenia (23% vs. 17%) were also increased in patients randomized to trastuzumab in combination with myelosuppressive chemotherapy as compared to chemotherapy alone. In Study 7 (metastatic gastric cancer) on the trastuzumab containing arm as compared to the chemotherapy alone arm, the incidence of NCI-CTC Grade 3/4 neutropenia was 36.8% compared to 28.9%; febrile neutropenia 5.1% compared to 2.8%.

Infection
The overall incidences of infection (46% vs. 30% [Study 5]), of selected NCI-CTC Grade 2 to 5 infection/febrile neutropenia (24.3% vs. 13.4% [Study 1]) and of selected Grade 3 to 5 infection/febrile neutropenia (2.9% vs. 1.4%) [Study 2]) were higher in patients receiving trastuzumab and chemotherapy compared with those receiving chemotherapy alone. The most common site of infections in the adjuvant setting involved the upper respiratory tract, skin, and urinary tract.

In Study 4, the overall incidence of infection was higher with the addition of trastuzumab to AC-T but not to TCH [44% (AC-TH), 37% (TCH), 38% (AC-T)]. The incidences of NCI-CTC Grade 3 to 4 infection were similar [25% (AC-TH), 21% (TCH), 23% (AC-T)] across the three arms.

In a randomized, controlled trial in treatment of metastatic breast cancer, the reported incidence of febrile neutropenia was higher (23% vs. 17%) in patients receiving trastuzumab in combination with myelosuppressive chemotherapy as compared to chemotherapy alone.

Pulmonary Toxicity
Adjuvant Breast Cancer
Among women receiving adjuvant therapy for breast cancer, the incidence of selected NCI-CTC Grade 2 to 5 pulmonary toxicity (14.3% vs. 5.4% [Study 1]) and of selected NCI-CTC Grade 3 to 5 pulmonary toxicity and spontaneous reported Grade 2 dyspnea (3.4 % vs. 0.9% [Study 2]) was

higher in patients receiving trastuzumab and chemotherapy compared with chemotherapy alone. The most common pulmonary toxicity was dyspnea (NCI-CTC Grade 2 to 5: 11.8% vs. 4.6% [Study 1]; NCI-CTC Grade 2 to 5: 2.4% vs. 0.2% [Study 2]).

Pneumonitis/pulmonary infiltrates occurred in 0.7% of patients receiving trastuzumab compared with 0.3% of those receiving chemotherapy alone. Fatal respiratory failure occurred in 3 patients receiving trastuzumab, one as a component of multi-organ system failure, as compared to 1 patient receiving chemotherapy alone.

In Study 3, there were 4 cases of interstitial pneumonitis in the one-year trastuzumab treatment arm compared to none in the observation arm at a median follow-up duration of 12.6 months.

Metastatic Breast Cancer
Among women receiving trastuzumab for treatment of metastatic breast cancer, the incidence of pulmonary toxicity was also increased. Pulmonary adverse events have been reported in the post-marketing experience as part of the symptom complex of infusion reactions. Pulmonary events include bronchospasm, hypoxia, dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema, and acute respiratory distress syndrome. For a detailed description, see *Warnings and Precautions (5.4)*.

Thrombosis/Embolism
In 4 randomized, controlled clinical trials, the incidence of thrombotic adverse events was higher in patients receiving trastuzumab and chemotherapy compared to chemotherapy alone in three studies (2.6% vs. 1.5% [Study 1], 2.5% and 3.7% vs. 2.2% [Study 4] and 2.1% vs. 0% [Study 5]).

Diarrhea
Among women receiving adjuvant therapy for breast cancer, the incidence of NCI-CTC Grade 2 to 5 diarrhea (6.7% vs. 5.4% [Study 1]) and of NCI-CTC Grade 3 to 5 diarrhea (2.2% vs. 0% [Study 2]), and of Grade 1 to 4 diarrhea (7% vs. 1% [Study 3; one-year trastuzumab treatment at 12.6 months median duration of follow-up]) were higher in patients receiving trastuzumab as compared to controls. In Study 4, the incidence of Grade 3 to 4 diarrhea was higher [5.7% AC-TH, 5.5% TCH vs. 3.0% AC-T] and of Grade 1 to 4 was higher [51% AC-TH, 63% TCH vs. 43% AC-T] among women receiving trastuzumab. Of patients receiving trastuzumab as a single agent for the treatment of metastatic breast cancer, 25% experienced diarrhea. An increased incidence of diarrhea was observed in patients receiving trastuzumab in combination with chemotherapy for treatment of metastatic breast cancer.

Renal Toxicity
In Study 7 (metastatic gastric cancer) on the trastuzumab-containing arm as compared to the chemotherapy alone arm the incidence of renal impairment was 18% compared to 14.5%. Severe (Grade 3/4) renal failure was 2.7% on the trastuzumab-containing arm compared to 1.7% on the chemotherapy only arm. Treatment discontinuation for renal insufficiency/failure was 2% on the trastuzumab-containing arm and 0.3% on the chemotherapy only arm.

In the post-marketing setting, rare cases of nephrotic syndrome with pathologic evidence of glomerulopathy have been reported. The time to onset ranged from 4 months to approximately 18

months from initiation of trastuzumab therapy. Pathologic findings included membranous glomerulonephritis, focal glomerulosclerosis, and fibrillary glomerulonephritis. Complications included volume overload and congestive heart failure.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other trastuzumab products may be misleading.
Among 903 women with metastatic breast cancer, human anti-human antibody (HAHA) to trastuzumab was detected in one patient using an enzyme-linked immunosorbent assay (ELISA). This patient did not experience an allergic reaction. Samples for assessment of HAHA were not collected in studies of adjuvant breast cancer.

6.3 Post-Marketing Experience

The following adverse reactions have been identified during post-approval use of trastuzumab. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

- Infusion reaction *[see Warnings and Precautions (5.2)]*
- Oligohydramnios or oligohydramnios sequence, including pulmonary hypoplasia, skeletal abnormalities, and neonatal death *[see Warnings and Precautions (5.3)]*
- Glomerulopathy *[see Adverse Reactions (6.1)]*
- Immune thrombocytopenia

7 DRUG INTERACTIONS

Patients who receive anthracycline after stopping trastuzumab products may be at increased risk of cardiac dysfunction because of trastuzumab's long washout period based on population PK analysis *[see Clinical Pharmacology (12.3)]*. If possible, physicians should avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab products. If anthracyclines are used, the patient's cardiac function should be monitored carefully.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Trastuzumab products can cause fetal harm when administered to a pregnant woman. In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death *(see Data)*. Apprise the patient of the potential risks to a fetus. There are clinical considerations if a trastuzumab product is used in a pregnant woman or if a patient becomes pregnant within 7 months following the last dose of a trastuzumab product *(see Clinical Considerations)*.

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Monitor women who received Ogivri during pregnancy or within 7 months prior to conception for oligohydramnios. If oligohydramnios occurs, perform fetal testing that is appropriate for gestational age and consistent with community standards of care.

Data

Human Data

In post-marketing reports, use of trastuzumab during pregnancy resulted in cases of oligohydramnios and of oligohydramnios sequence, manifesting in the fetus as pulmonary hypoplasia, skeletal abnormalities and neonatal death. These case reports described oligohydramnios in pregnant women who received trastuzumab either alone or in combination with chemotherapy. In some case reports, amniotic fluid index increased after trastuzumab was stopped. In one case, trastuzumab therapy resumed after amniotic index improved, and oligohydramnios recurred.

Animal Data

In studies where trastuzumab was administered to pregnant cynomolgus monkeys during the period of organogenesis at doses up to 25 mg/kg given twice weekly (up to 25 times the recommended weekly human dose of 2 mg/kg), trastuzumab crossed the placental barrier during the early (Gestation Days 20 to 50) and late (Gestation Days 120 to 150) phases of gestation. The resulting concentrations of trastuzumab in fetal serum and amniotic fluid were approximately 33% and 25%, respectively, of those present in the maternal serum but were not associated with adverse developmental effects.

8.2 Lactation

Risk Summary

There is no information regarding the presence of trastuzumab products in human milk, the effects on the breastfed infant, or the effects on milk production. Published data suggest human IgG is present in human milk but does not enter the neonatal and infant circulation in substantial amounts. Trastuzumab was present in the milk of lactating Cynomolgus monkeys but not associated with neonatal toxicity *(see Data)*. Consider the developmental and health benefits of breastfeeding along with the mother's clinical need for Ogivri treatment and any potential adverse effects on the breastfed child from Ogivri or from the underlying maternal condition. This consideration should also take into account the trastuzumab product wash out period of 7 months *[see Clinical Pharmacology (12.3)]*.

Data

In lactating cynomolgus monkeys, trastuzumab was present in breast milk at about 0.3% of maternal serum concentrations after pre-(beginning Gestation Day 120) and post-partum (through Post-partum Day 28) doses of 25 mg/kg administered twice weekly (25 times the recommended

weekly human dose of 2 mg/kg of trastuzumab products). Infant monkeys with detectable serum levels of trastuzumab did not exhibit any adverse effects on growth or development from birth to 1 month of age.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Verify the pregnancy status of females of reproductive potential prior to the initiation of Ogivri.

Contraception

Females

Trastuzumab products can cause embryo-fetal harm when administered during pregnancy. Advise females of reproductive potential to use effective contraception during treatment with Ogivri and for 7 months following the last dose of Ogivri *[see Use in Specific Populations (8.1) and Clinical Pharmacology (12.3)]*.

8.4 Pediatric Use

The safety and effectiveness of trastuzumab products in pediatric patients have not been established.

8.5 Geriatric Use

Trastuzumab has been administered to 386 patients who were 65 years of age or over (253 in the adjuvant treatment and 133 in metastatic breast cancer treatment settings). The risk of cardiac dysfunction was increased in geriatric patients as compared to younger patients in both those receiving treatment for metastatic disease in Studies 5 and 6, or adjuvant therapy in Studies 1 and 2. Limitations in data collection and differences in study design of the 4 studies of trastuzumab in adjuvant treatment of breast cancer preclude a determination of whether the toxicity profile of trastuzumab in older patients is different from younger patients. The reported clinical experience is not adequate to determine whether the efficacy improvements (ORR, TTP, OS, DFS) of trastuzumab treatment in older patients is different from that observed in patients < 65 years of age for metastatic disease and adjuvant treatment.

In Study 7 (metastatic gastric cancer), of the 294 patients treated with trastuzumab, 108 (37%) were 65 years of age or older, while 13 (4.4%) were 75 and over. No overall differences in safety or effectiveness were observed.

10 OVERDOSAGE

There is no experience with overdosage in human clinical trials. Single doses higher than 8 mg/kg have not been tested.

11 DESCRIPTION

Ogivri (trastuzumab-dkst) is a humanized IgG1 kappa monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor 2 protein, HER2. Trastuzumab-dkst is produced by recombinant DNA technology in a mammalian cell (Chinese Hamster Ovary) culture.

Ogivri (trastuzumab-dkst) is a sterile, off-white to pale yellow, preservative-free lyophilized powder for injection, for intravenous administration.

Each multiple-dose vial of Ogivri delivers 420 mg trastuzumab-dkst, 322.6 mg D-sorbitol, 6.0 mg L-Histidine, 9.4 mg L-Histidine hydrochloride monohydrate and 94.1 mg Polyethylene glycol 3350/Macrogol 3350. Reconstitution with 20 mL of the appropriate diluent (BWFI or SWFI) yields a solution containing 21 mg/mL trastuzumab-dkst that delivers 20 mL (420 mg trastuzumab-dkst), at a pH of approximately 6. If Ogivri is reconstituted with SWFI without preservative, the reconstituted solution is considered single-dose.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structurally related to the epidermal growth factor receptor. Trastuzumab products have been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor cells that overexpress HER2.

Trastuzumab products are mediators of antibody-dependent cellular cytotoxicity (ADCC). *In vitro*, trastuzumab product-mediated ADCC has been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do not overexpress HER2.

12.2 Pharmacodynamics

Cardiac Electrophysiology:

The effects of trastuzumab on electrocardiographic (ECG) endpoints, including QTc interval duration, were evaluated in patients with HER2 positive solid tumors. Trastuzumab had no clinically relevant effect on the QTc interval duration and there was no apparent relationship between serum trastuzumab concentrations and change in QTcF interval duration in patients with HER2 positive solid tumors.

12.3 Pharmacokinetics

The pharmacokinetics of trastuzumab were evaluated in a pooled population pharmacokinetic (PK) model analysis of 1,582 subjects with primarily breast cancer and metastatic gastric cancer (MGC) receiving intravenous trastuzumab. Total trastuzumab clearance increases with decreasing concentrations due to parallel linear and non-linear elimination pathways.

Although the average trastuzumab exposure was higher following the first cycle in breast cancer patients receiving the three-weekly schedule compared to the weekly schedule of trastuzumab, the average steady-state exposure was essentially the same at both dosages. The average trastuzumab exposure following the first cycle and at steady state as well as the time to steady state was higher in breast cancer patients compared to MGC patients at the same dosage; however, the reason for this exposure difference is unknown. Additional predicted trastuzumab exposure and PK parameters following the first trastuzumab cycle and at steady state exposure are described in Tables 7 and 8, respectively.

Population PK based simulations indicate that following discontinuation of trastuzumab, concentrations in at least 95% of breast cancer patients and MGC patients will decrease to

approximately 3% of the population predicted steady-state trough serum concentration (approximately 97% washout) by 7 months *[see Warnings and Precautions (5.1) and Use in Specific Populations (8.1, 8.3)]*.

Table 7
Population Predicted Cycle 1 PK Exposures (Median with 5th to 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	C_{min} (µg/mL)	C_{max} (µg/mL)	$AUC_{0\text{-}21days}$ (µg.day/mL)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	29.4 (5.8 to 59.5)	178 (117 to 291)	1373 (736 to 2245)
	MGC	274	23.1 (6.1 to50.3)	132 (84.2 to 225)	1109 (588 to 1938)
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	37.7 (12.3 to 70.9)	88.3 (58 to 144)	1066 (586 to 1754)

Table 8
Population Predicted Steady State PK Exposures (Median with 5th to 95th Percentiles) in Breast Cancer and MGC Patients

Schedule	Primary tumor type	N	$C_{min,ss}$[a] (µg/mL)	$C_{max,ss}$[b] (µg/mL)	$AUC_{ss,0\text{-}21days}$ (µg.day/mL)	Time to steady-state (week)	Total CL range at steady-state (L/day)
8 mg/kg + 6 mg/kg q3w	Breast cancer	1195	47.4 (5 to 115)	179 (107 to 309)	1794 (673 to 3618)	12	0.173 to 0.283
	MGC	274	32.9 (6.1 to 88.9)	131 (72.5 to 251)	1338 (557 to 2875)	9	0.189 to 0.337
4 mg/kg + 2 mg/kg qw	Breast cancer	1195	66.1 (14.9 to 142)	109 (51.0 to 209)	1765 (647 to 3578)	12	0.201 to 0.244

[a] Steady-state trough serum concentration of trastuzumab
[b] Maximum steady-state serum concentration of trastuzumab

Specific Populations: Based on a population pharmacokinetic analysis, no clinically significant differences were observed in the pharmacokinetics of trastuzumab based on age (<65 (n = 1294); ≥65 (n = 288)), race (Asian (n = 264); non-Asian (n = 1324)) and renal impairment (mild (creatinine clearance [CLcr] 60 to 90 mL/min) (n = 636) or moderate (CLcr 30 to 60 mL/min) (n = 133)). The pharmacokinetics of trastuzumab products in patients with severe renal impairment, end-stage renal disease with or without hemodialysis, or hepatic impairment is unknown.

***Drug Interaction Studies*:** There have been no formal drug interaction studies performed with trastuzumab products in humans. Clinically significant interactions between trastuzumab and concomitant medications used in clinical trials have not been observed.

Paclitaxel and doxorubicin: Concentrations of paclitaxel and doxorubicin and their major metabolites (i.e., 6-α hydroxyl-paclitaxel [POH], and doxorubicinol [DOL], respectively) were not altered in the presence of trastuzumab when used as combination therapy in clinical trials. Trastuzumab concentrations were not altered as part of this combination therapy.

Docetaxel and carboplatin: When trastuzumab was administered in combination with docetaxel or carboplatin, neither the plasma concentrations of docetaxel or carboplatin nor the plasma concentrations of trastuzumab were altered.

Cisplatin and capecitabine: In a drug interaction substudy conducted in patients in Study 7, the pharmacokinetics of cisplatin, capecitabine and their metabolites were not altered when administered in combination with trastuzumab.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Trastuzumab products have not been tested for carcinogenic potential.

No evidence of mutagenic activity was observed when trastuzumab was tested in the standard Ames bacterial and human peripheral blood lymphocyte mutagenicity assays, at concentrations of up to 5000 mcg/mL. In an *in vivo* micronucleus assay, no evidence of chromosomal damage to mouse bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg of trastuzumab.

A fertility study was conducted in female cynomolgus monkeys at doses up to 25 times the weekly recommended human dose of 2 mg/kg of trastuzumab and has revealed no evidence of impaired fertility, as measured by menstrual cycle duration and female sex hormone levels.

14 CLINICAL STUDIES

14.1 Adjuvant Breast Cancer

The safety and efficacy of trastuzumab in women receiving adjuvant chemotherapy for HER2 overexpressing breast cancer were evaluated in an integrated analysis of two randomized, open-label, clinical trials (Studies 1 and 2) with a total of 4063 women at the protocol-specified final overall survival analysis, a third randomized, open-label, clinical trial (Study 3) with a total of 3386 women at definitive Disease-Free Survival analysis for one-year trastuzumab treatment versus observation, and a fourth randomized, open-label clinical trial with a total of 3222 patients (Study 4).

Studies 1 and 2:

In Studies 1 and 2, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH). HER2 testing was verified by a central laboratory prior to randomization (Study 2) or was required to be performed at a reference laboratory (Study 1). Patients with a history of active cardiac disease based on symptoms, abnormal electrocardiographic, radiologic, or left ventricular ejection fraction findings or uncontrolled hypertension (diastolic > 100 mm Hg or systolic > 200 mm Hg) were not eligible.

Patients were randomized (1:1) to receive doxorubicin and cyclophosphamide followed by paclitaxel (AC → paclitaxel) alone or paclitaxel plus trastuzumab (AC → paclitaxel + trastuzumab). In both trials, patients received four 21-day cycles of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2. Paclitaxel was administered either weekly (80 mg/m^2) or every 3 weeks (175 mg/m^2) for a total of 12 weeks in Study 1; paclitaxel was administered only by the weekly schedule in Study 2. Trastuzumab was administered at 4 mg/kg on the day of initiation of paclitaxel and then at a dose of 2 mg/kg weekly for a total of 52 weeks. Trastuzumab treatment was permanently discontinued in patients who developed congestive heart failure, or persistent/recurrent LVEF decline *[see Dosage and Administration (2.3)]*. Radiation therapy, if administered, was initiated after the completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. The primary endpoint of the combined efficacy analysis was Disease-Free Survival (DFS), defined as the time from randomization to recurrence, occurrence of contralateral breast cancer, other second primary cancer, or death. The secondary endpoint was overall survival (OS).

A total of 3752 patients were included in the joint efficacy analysis of the primary endpoint of DFS following a median follow-up of 2.0 years in the AC → paclitaxel + trastuzumab arm. The pre-planned final OS analysis from the joint analysis included 4063 patients and was performed when 707 deaths had occurred after a median follow-up of 8.3 years in the AC → paclitaxel + trastuzumab arm. The data from both arms in Study 1 and two of the three study arms in Study 2 were pooled for efficacy analyses. The patients included in the primary DFS analysis had a median age of 49 years (range, 22 to 80 years; 6% > 65 years), 84% were white, 7% black, 4% Hispanic, and 4% Asian/Pacific Islander. Disease characteristics included 90% infiltrating ductal histology, 38% T1, 744 91% nodal involvement, 27% intermediate and 66% high grade pathology, and 53% ER+ and/or PR+ tumors. Similar demographic and baseline characteristics were reported for the efficacy evaluable population, after 8.3 years of median follow-up in the AC → paclitaxel + trastuzumab arm.

Study 3:
In Study 3, breast tumor specimens were required to show HER2 overexpression (3+ by IHC) or gene amplification (by FISH) as determined at a central laboratory. Patients with node-negative disease were required to have ≥ T1c primary tumor. Patients with a history of congestive heart failure or LVEF < 55%, uncontrolled arrhythmias, angina requiring medication, clinically significant valvular heart disease, evidence of transmural infarction on ECG, poorly controlled hypertension (systolic > 180 mm Hg or diastolic > 100 mm Hg) were not eligible.

Study 3 was designed to compare one and two years of three-weekly trastuzumab treatment versus observation in patients with HER2 positive EBC following surgery, established chemotherapy and radiotherapy (if applicable). Patients were randomized (1:1:1) upon completion of definitive surgery, and at least four cycles of chemotherapy to receive no additional treatment, or one year of trastuzumab treatment or two years of trastuzumab treatment. Patients undergoing a lumpectomy had also completed standard radiotherapy. Patients with ER+ and/or PgR+ disease received systemic adjuvant hormonal therapy at investigator discretion. Trastuzumab was administered with an initial dose of 8 mg/kg followed by subsequent doses of 6 mg/kg once every three weeks. The main outcome measure was Disease-Free Survival (DFS), defined as in Studies 1 and 2.

A protocol specified interim efficacy analysis comparing one-year trastuzumab treatment to observation was performed at a median follow-up duration of 12.6 months in the trastuzumab arm and formed the basis for the definitive DFS results from this study. Among the 3386 patients randomized to the observation (n = 1693) and trastuzumab one-year (n = 1693) treatment arms, the median age was 49 years (range 21 to 80), 83% were Caucasian, and 13% were Asian. Disease characteristics: 94% infiltrating ductal carcinoma, 50% ER+ and/or PgR+, 57% node positive, 32% node negative, and in 11% of patients, nodal status was not assessable due to prior neo-adjuvant chemotherapy. Ninety-six percent (1055/1098) of patients with node-negative disease had high-risk features: among the 1098 patients with node-negative disease, 49% (543) were ER− and PgR−, and 47% (512) were ER and/or PgR + and had at least one of the following high-risk features: pathological tumor size greater than 2 cm, Grade 2 to 3, or age <35 years. Prior to randomization, 94% of patients had received anthracycline-based chemotherapy regimens.

After the definitive DFS results comparing observation to one-year trastuzumab treatment were disclosed, a prospectively planned analysis that included comparison of one year versus two years of trastuzumab treatment at a median follow-up duration of 8 years was performed. Based on this analysis, extending trastuzumab treatment for a duration of two years did not show additional benefit over treatment for one year [Hazard Ratios of two-years trastuzumab versus one-year trastuzumab treatment in the intent to treat (ITT) population for Disease-Free Survival (DFS) = 0.99 (95% CI: 0.87, 1.13), p-value = 0.90 and Overall Survival (OS) = 0.98 (0.83, 1.15); p-value = 0.78].

Study 4:
In Study 4, breast tumor specimens were required to show HER2 gene amplification (FISH+ only) as determined at a central laboratory. Patients were required to have either node-positive disease, or node-negative disease with at least one of the following high-risk features: ER/PR-negative, tumor size > 2 cm, age < 35 years, or histologic and/or nuclear Grade 2 or 3. Patients with a history of CHF, myocardial infarction, Grade 3 or 4 cardiac arrhythmia, angina requiring medication, clinically significant valvular heart disease, poorly controlled hypertension (diastolic > 100 mm Hg), any T4 or N2 or known N3 or M1 breast cancer were not eligible.

Patients were randomized (1:1:1) to receive doxorubicin and cyclophosphamide followed by docetaxel (AC-T), doxorubicin and cyclophosphamide followed by docetaxel plus trastuzumab (AC-TH), or docetaxel and carboplatin plus trastuzumab (TCH). In both the AC-T and AC-TH arms, doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 were administered every 3 weeks for four cycles; docetaxel 100 mg/m^2 was administered every 3 weeks for four cycles. In the TCH arm, docetaxel 75 mg/m^2 and carboplatin (at a target AUC of 6 mg/mL/min as a 30-to 60-minute infusion) were administered every 3 weeks for six cycles. Trastuzumab was administered weekly (initial dose of 4 mg/kg followed by weekly dose of 2 mg/kg) concurrently with either T or TC, and then every 3 weeks (6 mg/kg) as monotherapy for a total of 52 weeks. Radiation therapy, if administered, was initiated after completion of chemotherapy. Patients with ER+ and/or PR+ tumors received hormonal therapy. Disease-Free Survival (DFS) was the main outcome measure.

Among the 3222 patients randomized, the median age was 49 (range 22 to 74 years; 6% ≥ 65 years). Disease characteristics included 54% ER+ and/or PR+ and 71% node positive. Prior to randomization, all patients underwent primary surgery for breast cancer.

The results for DFS for the integrated analysis of Studies 1 and 2, Study 3, and Study 4 and OS results for the integrated analysis of Studies 1 and 2, and Study 3 are presented in Table 9. For Studies 1 and 2, the duration of DFS following a median follow-up of 2.0 years in the AC → TH arm is presented in Figure 4, and the duration of OS after a median follow-up of 8.3 years in the AC → TH arm is presented in Figure 5. The duration of DFS for Study 4 is presented in Figure 6. Across all four studies, at the time of definitive DFS analysis, there were insufficient numbers of patients within each of the following subgroups to determine if the treatment effect was different from that of the overall patient population: patients with low tumor grade, patients within specific ethnic/racial subgroups (Black, Hispanic, Asian/Pacific Islander patients), and patients > 65 years of age. For Studies 1 and 2, the OS hazard ratio was 0.64 (95% CI: 0.55, 0.74). At 8.3 years of median follow-up [AC → TH], the survival rate was estimated to be 86.9% in the AC → TH arm and 79.4% in the AC → T arm. The final OS analysis results from Studies 1 and 2 indicate that OS benefit by age, hormone receptor status, number of positive lymph nodes, tumor size and grade, and surgery/radiation therapy was consistent with the treatment effect in the overall population. In patients ≤ 50 years of age (n = 2197), the OS hazard ratio was 0.65 (95% CI: 0.52, 0.81) and in patients > 50 years of age (n = 1866), the OS hazard ratio was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-positive disease (ER-positive and/or PR-positive) (n = 2223), the hazard ratio for OS was 0.63 (95% CI: 0.51, 0.78). In the subgroup of patients with hormone receptor-negative disease (ER-negative and PR-negative) (n = 1830), the hazard ratio for OS was 0.64 (95% CI: 0.52, 0.80). In the subgroup of patients with tumor size ≤ 2 cm (n = 1604), the hazard ratio for OS was 0.52 (95% CI: 0.39, 0.71). In the subgroup of patients with tumor size > 2 cm (n = 2448), the hazard ratio for OS was 0.67 (95% CI: 0.56, 0.80).

Table 9
Efficacy Results from Adjuvant Treatment of
Breast Cancer (Studies 1 + 2, Study 3, and Study 4)

	DFS events	DFS Hazard ratio (95% CI) p-value	Deaths (OS events)	OS Hazard ratio p-value
Studies 1 + 2[a]				
AC → TH (n = 1872)[b] (n = 2031)[c]	133[b]	0.48[b,d] (0.39, 0.59) p < 0.0001[e]	289[c]	0.64[c,d] (0.55, 0.74) p < 0.0001[e]
AC → T (n = 1880)[b] (n = 2032)[c]	261[b]		418[c]	
Study 3[f]				
Chemo →	127	0.54	31	0.75

Trastuzumab (n = 1693)		(0.44, 0.67) p < 0.0001[g]		p = NS[h]
Chemo → Observation (n = 1693)	219		40	
Study 4[i]				
TCH (n = 1075)	134	0.67 (0.54 to 0.84) p = 0.0006[e,j]	56	
AC → TH (n = 1074)	121	0.60 (0.48 to 0.76) p < 0.0001[e,i]	49	
AC → T (n = 1073)	180		80	

CI = confidence interval.

[a] Studies 1 and 2 regimens: doxorubicin and cyclophosphamide followed by paclitaxel (AC → T) or paclitaxel plus trastuzumab (AC → TH).

[b] Efficacy evaluable population, for the primary DFS analysis, following a median follow-up of 2.0 years in the AC → TH arm.

[c] Efficacy evaluable population, for the final OS analysis, following 707 deaths (8.3 years of median follow-up in the AC → TH arm).

[d] Hazard ratio estimated by Cox regression stratified by clinical trial, intended paclitaxel schedule, number of positive nodes, and hormone receptor status.

[e] stratified log-rank test.

[f] At definitive DFS analysis with median duration of follow-up of 12.6 months in the one-year trastuzumab treatment arm.

[g] log-rank test.

[h] NS = non-significant.

[i] Study 4 regimens: doxorubicin and cyclophosphamide followed by docetaxel (AC → T) or docetaxel plus trastuzumab (AC → TH); docetaxel and carboplatin plus trastuzumab (TCH).

[j] two-sided alpha level of 0.025 for each comparison.

Figure 4
Duration of Disease-Free Survival in
Patients with Adjuvant Treatment of Breast Cancer (Studies 1 and 2)

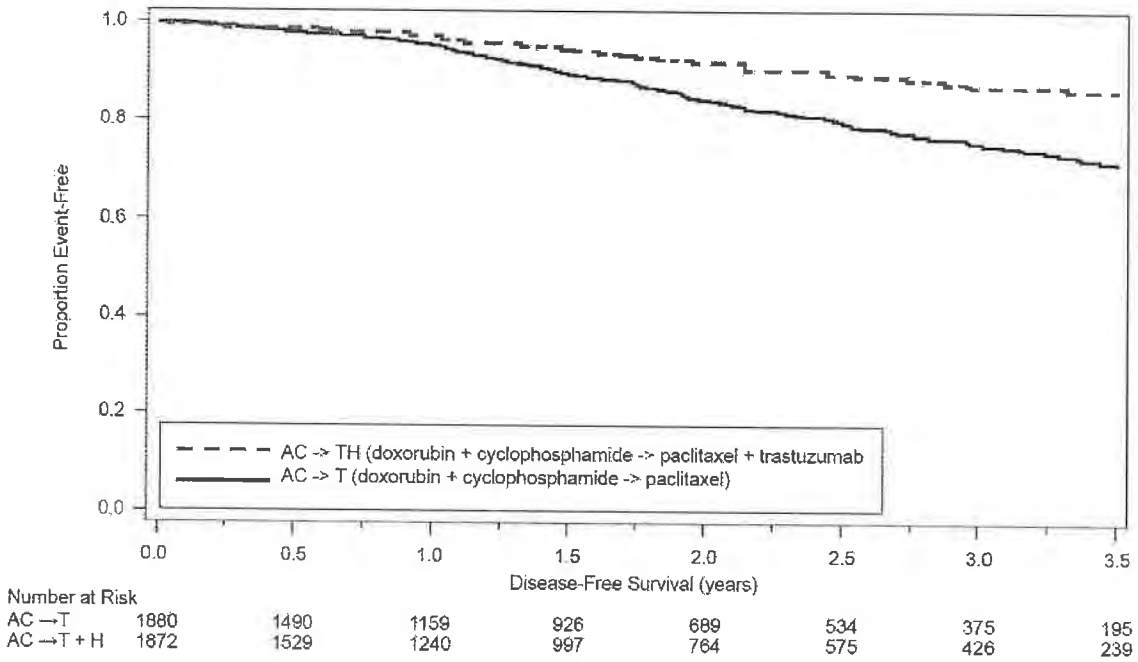


Figure 5
Duration of Overall Survival in Patients with
Adjuvant Treatment of Breast Cancer (Studies 1 and 2)

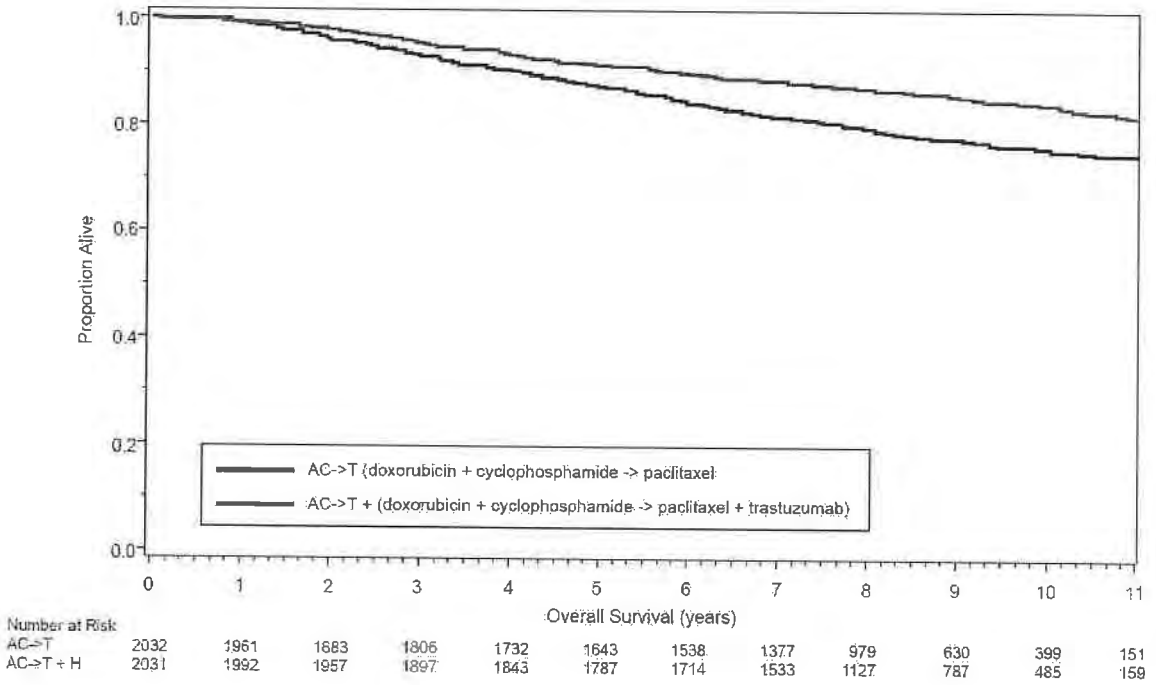
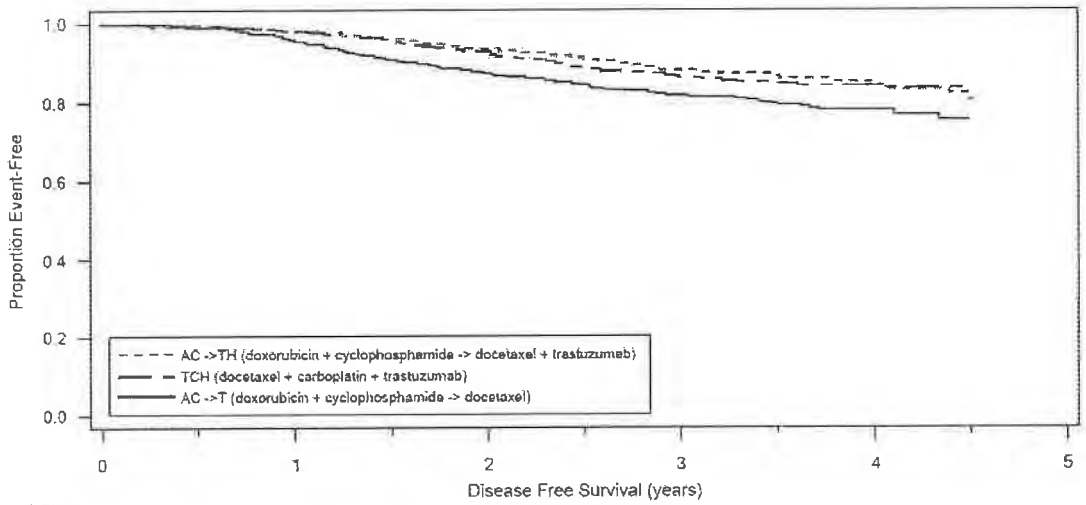


Figure 6
Duration of Disease-Free Survival in Patients with
Adjuvant Treatment of Breast Cancer (Study 4)



Number at Risk

AC->T	1073	971	802	417	103
AC->TH	1074	1023	885	457	126
TCH	1075	1018	877	447	126

AC=doxorubicin and cyclophosphamide; T=docetaxel; TCH=docetaxel, platinum salt, and trastuzumab; TH=docetaxel and trastuzumab
Kaplan-Meier estimates are shown.

Exploratory analyses of DFS as a function of HER2 overexpression or gene amplification were conducted for patients in Studies 2 and 3, where central laboratory testing data were available. The results are shown in Table 10. The number of events in Study 2 was small with the exception of the IHC 3+/FISH+ subgroup, which constituted 81% of those with data. Definitive conclusions cannot be drawn regarding efficacy within other subgroups due to the small number of events. The number of events in Study 3 was adequate to demonstrate significant effects on DFS in the IHC 3+/FISH unknown and the FISH +/IHC unknown subgroups.

Table 10
Treatment Outcomes in Studies 2 and 3 as a Function of
HER2 Overexpression or Amplification

	Study 2		Study 3[c]	
HER2 Assay Result[a]	Number of Patients	Hazard Ratio DFS (95% CI)	Number of Patients	Hazard Ratio DFS (95% CI)
IHC 3+				
FISH (+)	1170	0.42 (0.27, 0.64)	91	0.56 (0.13, 2.50)
FISH (–)	51	0.71 (0.04, 11.79)	8	—
FISH Unknown	51	0.69 (0.09, 5.14)	2258	0.53 (0.41, 0.69)

IHC < 3+ / FISH (+)	174	1.01 (0.18, 5.65)	299[b]	0.53 (0.20, 1.42)
IHC unknown / FISH (+)	—	—	724	0.59 (0.38, 0.93)

[a] IHC by HercepTest, FISH by PathVysion (HER2/CEP17 ratio ≥ 2.0) as performed at a central laboratory.
[b] All cases in this category in Study 3 were IHC 2+.
[c] Median follow-up duration of 12.6 months in the one-year trastuzumab treatment arm.

14.2 Metastatic Breast Cancer

The safety and efficacy of trastuzumab in treatment of women with metastatic breast cancer were studied in a randomized, controlled clinical trial in combination with chemotherapy (Study 5, n = 469 patients) and an open-label single agent clinical trial (Study 6, n = 222 patients). Both trials studied patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Patients were eligible if they had 2 or 3 levels of overexpression (based on a 0 to 3 scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

Previously Untreated Metastatic Breast Cancer (Study 5):

Study 5 was a multicenter, randomized, open-label clinical trial conducted in 469 women with metastatic breast cancer who had not been previously treated with chemotherapy for metastatic disease. Tumor specimens were tested by IHC (Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+, with 3+ indicating the strongest positivity. Only patients with 2+ or 3+ positive tumors were eligible (about 33% of those screened). Patients were randomized to receive chemotherapy alone or in combination with trastuzumab given intravenously as a 4 mg/kg loading dose followed by weekly doses of trastuzumab at 2 mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of paclitaxel (175 mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 21 days for six cycles). Sixty-five percent of patients randomized to receive chemotherapy alone in this study received trastuzumab at the time of disease progression as part of a separate extension study.

Based upon the determination by an independent response evaluation committee the patients randomized to trastuzumab and chemotherapy experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), and a longer median duration of response, as compared with patients randomized to chemotherapy alone. Patients randomized to trastuzumab and chemotherapy also had a longer median survival (see Table 11). These treatment effects were observed both in patients who received trastuzumab plus paclitaxel and in those who received trastuzumab plus AC; however the magnitude of the effects was greater in the paclitaxel subgroup.

Table 11
Study 5: Efficacy Results in
First-Line Treatment for Metastatic Breast Cancer

	Combined Results		Paclitaxel Subgroup		AC Subgroup	
	trastuzumab + All Chemo-	All Chemo-	trastuzumab + Paclitaxel	Paclitaxel (n = 96)	trastuzumab + AC[a]	AC (n =

	therapy (n = 235)	therapy (n = 234)	(n = 92)		(n = 143)	138)
Primary Endpoint						
Median TTP(mos)[b,c]	7.2	4.5	6.7	2.5	7.6	5.7
95% CI	7, 8	4, 5	5, 10	2, 4	7, 9	5, 7
p-value[d]	< 0.0001		< 0.0001		0.002	
Secondary Endpoints						
Overall Response Rate[b]	45	29	38	15	50	38
95% CI	39, 51	23, 35	28, 48	8, 22	42, 58	30, 46
p-value[e]	< 0.001		< 0.001		0.10	
Median Resp Duration (mos)[b,c]	8.3	5.8	8.3	4.3	8.4	6.4
25%, 75% Quartile	6, 15	4, 8	5, 11	4, 7	6, 15	4, 8
Med Survival (mos)[c]	25.1	20.3	22.1	18.4	26.8	21.4
95% CI	22, 30	17, 24	17, 29	13, 24	23, 33	18, 27
p-value[d]	0.05		0.17		0.16	

[a] AC = Anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate.
[d] log-rank test.
[e] $\chi 2$-test.

Data from Study 5 suggest that the beneficial treatment effects were largely limited to patients with the highest level of HER2 protein overexpression (3+) (see Table 12).

Table 12
Treatment Effects in Study 5 as a
Function of HER2 Overexpression or Amplification

HER2 Assay Result	Number of Patients (N)	Relative Risk[b] for Time to Disease Progression (95% CI)	Relative Risk[b] for Mortality (95% CI)
CTA 2+ or 3+	469	0.49 (0.40, 0.61)	0.80 (0.64, 1.00)
FISH (+)[a]	325	0.44 (0.34, 0.57)	0.70 (0.53, 0.91)
FISH (−)[a]	126	0.62 (0.42, 0.94)	1.06 (0.70, 1.63)
CTA 2+	120	0.76 (0.50, 1.15)	1.26 (0.82, 1.94)

FISH (+)	32	0.54 (0.21, 1.35)	1.31 (0.53, 3.27)
FISH (−)	83	0.77 (0.48, 1.25)	1.11 (0.68, 1.82)
CTA 3+	349	0.42 (0.33, 0.54)	0.70 (0.51, 0.90)
FISH (+)	293	0.42 (0.32, 0.55)	0.67 (0.51, 0.89)
FISH (−)	43	0.43 (0.20, 0.94)	0.88 (0.39, 1.98)

[a] FISH testing results were available for 451 of the 469 patients enrolled on study.
[b] The relative risk represents the risk of progression or death in the trastuzumab plus chemotherapy arm versus the chemotherapy arm.

Previously Treated Metastatic Breast Cancer (Study 6):
Trastuzumab was studied as a single agent in a multicenter, open-label, single-arm clinical trial (Study 6) in patients with HER2 overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for metastatic disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior chemotherapy regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. Patients were treated with a loading dose of 4 mg/kg IV followed by weekly doses of trastuzumab at 2 mg/kg IV.

The ORR (complete response + partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% complete response rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to skin and lymph nodes. The overall response rate in patients whose tumors tested as CTA 3+ was 18% while in those that tested as CTA 2+, it was 6%.

14.3 Metastatic Gastric Cancer
The safety and efficacy of trastuzumab in combination with cisplatin and a fluoropyrimidine (capecitabine or 5-fluorouracil) were studied in patients previously untreated for metastatic gastric or gastroesophageal junction adenocarcinoma (Study 7). In this open-label, multi-center trial, 594 patients were randomized 1:1 to trastuzumab in combination with cisplatin and a fluoropyrimidine (FC+T) or chemotherapy alone (FC). Randomization was stratified by extent of disease (metastatic vs. locally advanced), primary site (gastric vs. gastroesophageal junction), tumor measurability (yes vs. no), ECOG performance status (0,1 vs. 2), and fluoropyrimidine (capecitabine vs. 5-fluorouracil). All patients were either HER2 gene amplified (FISH+) or HER2 overexpressing (IHC 3+). Patients were also required to have adequate cardiac function (e.g., LVEF > 50%).

On the trastuzumab-containing arm, trastuzumab was administered as an IV infusion at an initial dose of 8 mg/kg followed by 6 mg/kg every 3 weeks until disease progression. On both study arms cisplatin was administered at a dose of 80 mg/m^2 Day 1 every 3 weeks for 6 cycles as a 2 hour IV infusion. On both study arms capecitabine was administered at 1000 mg/m^2 dose orally twice daily (total daily dose 2000 mg/m^2) for 14 days of each 21 day cycle for 6 cycles. Alternatively, continuous intravenous infusion (CIV) 5-fluorouracil was administered at a dose of 800 mg/m^2/day from Day 1 through Day 5 every three weeks for 6 cycles.

The median age of the study population was 60 years (range: 21–83); 76% were male; 53% were Asian, 38% Caucasian, 5% Hispanic, 5% other racial/ethnic groups; 91% had ECOG PS of 0 or 1; 82% had primary gastric cancer and 18% had primary gastroesophageal adenocarcinoma. Of these patients, 23% had undergone prior gastrectomy, 7% had received prior neoadjuvant and/or adjuvant therapy, and 2% had received prior radiotherapy.

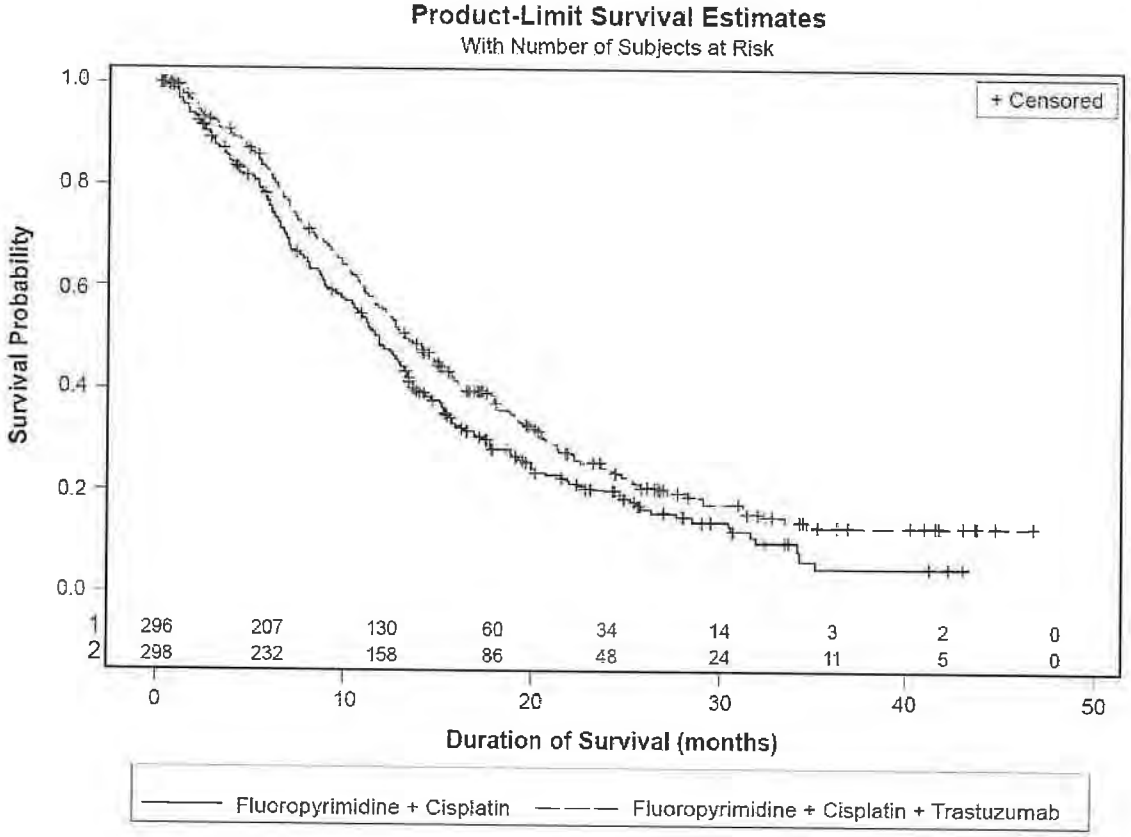
The main outcome measure of Study 7 was overall survival (OS), analyzed by the unstratified log-rank test. The final OS analysis based on 351 deaths was statistically significant (nominal significance level of 0.0193). An updated OS analysis was conducted at one year after the final analysis. The efficacy results of both the final and the updated analyses are summarized in Table 13 and Figure 7.

Table 13
Study 7: Overall Survival in ITT Population

	FC Arm N = 296		FC + T Arm N = 298
Definitive (Second Interim) Overall Survival			
No. Deaths (%)	184 (62.2%)		167 (56.0%)
Median	11.0		13.5
95% CI (mos.)	(9.4, 12.5)		(11.7, 15.7)
Hazard Ratio		0.73	
95% CI		(0.60, 0.91)	
p-value*, two-sided		0.0038	
Updated Overall Survival			
No. Deaths (%)	227 (76.7%)		221 (74.2%)
Median	11.7		13.1
95% CI (mos.)	(10.3, 13.0)		(11.9, 15.1)
Hazard Ratio		0.80	
95% CI		(0.67, 0.97)	

*Comparing with the nominal significance level of 0.0193.

Figure 7
Updated Overall Survival in Patients with Metastatic Gastric Cancer (Study 7)



An exploratory analysis of OS in patients based on HER2 gene amplification (FISH) and protein overexpression (IHC) testing is summarized in Table 14.

Table 14
Exploratory analyses by HER2 Status Using Updated Overall survival Results

	FC (N = 296)[a]		FC + T (N = 298)[b]
FISH+ / IHC 0, 1+ subgroup (N = 133)			
No. Deaths (%) / n (%)	57/71 (80%)		56/62 (90%)
Median OS Duration (mos.)	8.8		8.3

95% CI (mos.)	(6.4, 11.7)		(6.2, 10.7)
Hazard Ratio (95% CI)		1.33 (0.92, 1.92)	
FISH+ / IHC2+ subgroup (N = 160)			
No. Deaths (%) / n (%)	65/80 (81%)		64/80 (80%)
Median OS Duration (mos.)	10.8		12.3
95% CI (mos.)	(6.8, 12.8)		(9.5, 15.7)
Hazard Ratio (95% CI)		0.78 (0.55, 1.10)	
FISH+ or FISH-/ IHC3+[c] subgroup (N = 294)			
No. Deaths (%) / n (%)	104/143 (73%)		96/151 (64%)
Median OS Duration (mos.)	13.2		18.0
95% CI (mos.)	(11.5, 15.2)		(15.5, 21.2)
Hazard Ratio (95% CI)		0.66 (0.50, 0.87)	

[a] Two patients on the FC arm who were FISH+ but IHC status unknown were excluded from the exploratory subgroup analyses.
[b] Five patients on the trastuzumab-containing arm who were FISH+, but IHC status unknown were excluded from the exploratory subgroup analyses.
[c] Includes 6 patients on chemotherapy arm, 10 patients on trastuzumab arm with FISH–, IHC3+ and 8 patients on chemotherapy arm, 8 patients on trastuzumab arm with FISH status unknown, IHC 3+.

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

Ogivri (trastuzumab-dkst) for injection 420 mg/vial is supplied in a multiple-dose vial as an off-white to pale yellow lyophilized sterile powder, under vacuum. Each carton contains one multiple-dose vial of Ogivri and one vial (20 mL) of Bacteriostatic Water for Injection (BWFI), USP, containing 1.1% benzyl alcohol as a preservative.

NDC 67457-847-44

16.2 Storage

Store Ogivri vials in the refrigerator at 2° to 8°C (36° to 46°F) until time of reconstitution

17 PATIENT COUNSELING INFORMATION

Cardiomyopathy

- Advise patients to contact a health care professional immediately for any of the following: new onset or worsening shortness of breath, cough, swelling of the ankles/legs, swelling of the face, palpitations, weight gain of more than 5 pounds in 24 hours, dizziness or loss of consciousness *[see Boxed Warning: Cardiomyopathy]*.

Embryo-Fetal Toxicity

- Advise pregnant women and females of reproductive potential that Ogivri exposure during pregnancy or within 7 months prior to conception can result in fetal harm. Advise female patients to contact their healthcare provider with a known or suspected pregnancy *[see Use in Specific Populations (8.1)]*.

- Advise females of reproductive potential to use effective contraception during treatment and for 7 months following the last dose of Ogivri *[see Use in Specific Populations (8.3)]*.

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EXHIBIT 25

BIOLOGICS AND BIOSIMILARS: BALANCING INCENTIVES FOR INNOVATION

HEARING

BEFORE THE

SUBCOMMITTEE ON COURTS AND COMPETITION POLICY

OF THE

COMMITTEE ON THE JUDICIARY
HOUSE OF REPRESENTATIVES

ONE HUNDRED ELEVENTH CONGRESS

FIRST SESSION

JULY 14, 2009

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CONTENTS

JULY 14, 2009

APPENDIX

MATERIAL SUBMITTED FOR THE HEARING RECORD

BIOLOGICS AND BIOSIMILARS: BALANCING INCENTIVES FOR INNOVATION

TUESDAY, JULY 14, 2009

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON COURTS AND
COMPETITION POLICY
COMMITTEE ON THE JUDICIARY,
Washington, DC.

The Subcommittee met, pursuant to notice, at 2:20 p.m., in room 2141, Rayburn House Office Building, the Honorable Henry C. "Hank" Johnson, Jr. (Chairman of the Subcommittee) presiding.

Present: Representatives Johnson, Gonzalez, Jackson Lee, Watt, Sherman, Issa, Goodlatte, and Coble.

Staff Present: (Majority) Christal Sheppard, Subcommittee Chief Counsel; Eric Garduno, Counsel; Rosalind Jackson, Professional Staff Member; (Minority) and Blaine Merritt, Counsel.

Mr. JOHNSON. This hearing of the Subcommittee on Courts and Competition Policy will now come to order.

Without objection, the Chair will be authorized to declare a recess of the hearing.

Under current law, generic versions of the chemical pharmaceutical products may be introduced through an expedited pathway that allows generic makers to rely on the safety and efficacy test data of an original Food-and-Drug-Administration-approved drug. This dramatically reduces the cost of entry for generics, which has translated into substantial savings to customers. The Congressional Budget Office has estimated that consumers save $8 billion to $10 billion a year, thanks to the price competition from generics.

There is, however, no equivalent statutory pathway for generic versions of biological pharmaceutical products, otherwise known as biosimilars. Congress has explored the creation of a generic pathway for biosimilars for some time, but it wasn't until this Congress that real momentum has built behind such a legislative endeavor. This is in large part due to the effort by Congress and the Obama administration to pass comprehensive health care reform. Many believe that establishing a pathway for biosimilars will contribute to our efforts to reduce the cost of health care.

Creation of a pathway for biosimilars has been a contentious issue. Much of the debate concerning such a pathway revolves around whether the science is perfected enough to determine if a biosimilar that relies on an innovator's test data will have the same health benefits as the innovator drug without additional health risks. Additional concerns center on the intellectual property

protections afforded drug innovators and how the nature of those protections will impact competition, future biotechnology industry investment and the cost of biological pharmaceutical products.

It is, without a doubt, that the development of new biologics is an expensive endeavor. Estimates put average development costs as much as $1.37 billion. It is also without a doubt that the cost of pharmaceutical products, and in particular biologics, is huge. In 2007, pharmaceutical expenditures accounted for $231.3 billion in health care costs, and biologics represented $40.3 billion of this total.

The question before us today is how to frame the intellectual property protections in a pathway for biosimilars that incentivizes the extraordinary investment required to develop new biologics but does not discourage biosimilar introduction.

I look forward to our hearing with the distinguished witnesses that we have on board who will comment on whether there should be a long data exclusivity period that significantly delays biosimilar competition, whether biotechnology patents are broad enough to apply to biosimilar products and processes, and the extent to which other factors provide market-entry barriers that will limit biosimilar entry and thereby protect innovators.

I now recognize my colleague, Mr. Howard Coble, the distinguished Ranking Member of the Subcommittee on Courts and Competition Policy for his opening remarks.

Mr. COBLE. Thank you, Mr. Chairman, and I thank you for having called the hearing which addresses an important health care issue and directly affects subject matter that is a portion of the Judiciary Committee's jurisdiction.

Mr. Chairman, I will try not to be too verbose, but this subject is very detailed and very complex; perhaps not so detailed and complex to the scientifically adept, but I belong to the scientifically inept group, and to me, it is very complex.

The Hatch-Waxman Act, which is almost a quarter century old, gave birth to the generic chemical drug industry, as we all know. By most accounts, it has worked well by balancing the interests of brand manufacturers, generic companies, and patients. It has generated greater price competition in the pharmaceutical industry without destroying the incentive for brands to conduct further research and roll out new products that benefit patients worldwide.

In recent years, Mr. Chairman, legislators and other health care experts have contemplated the creation of a similar legislative pathway for a generic biologics industry. This discussion not only resurrects some of the same issues confronting Congress during consideration of Hatch-Waxman, it also invites debate over the wisdom of using Hatch-Waxman as an appropriate template for biosimilars.

As I said at the outset, I am no expert in the fields of biology, chemistry, or recombinant DNA, but I do understand the basic difference between chemical pharmaceuticals and biologics.

Chemical drugs are usually produced in pill form. They are chemically synthesized and comprised of small molecules. Compared to biologics, chemical pharmaceuticals are far easier to manufacture and replicate.

Biologics are made, as we know, from living organisms. They are normally comprised of protein and are increasingly a part of recombinant DNA research and production. Their characteristic properties include a high molecular weight, varying levels of hard-to-remove biological impurities, and a high degree of sensitivity to environmental conditions. The manufacturing process is therefore critical to the final product. This complexity means one cannot guarantee that reproduction of a biological drug results in an exact duplicate.

This is not the case for chemical pharmaceuticals regulated under Hatch-Waxman since it is chemically identical to the innovator drug. That is why the term generic biologic is technically inaccurate, it seems to me. Biosimilar or follow-on biologic would be preferred.

In our quest to develop a legislative pathway for biosimilars, we must keep these differences in mind. While the Judiciary Committee's jurisdiction does not include public health and related safety issues, all Members, whatever their Committee assignments, cannot discharge the importance of protecting patients. Any bill we end up supporting cannot sacrifice public safety on the alter of potential cost savings.

I have some more to say, Mr. Chairman, but in the interest of time, I would ask unanimous consent to have my entire statement put into the record, and we hope that we will have a balanced and talented roster of witnesses, which we will have, who will add to our understanding of this complex subject.

I look forward to participating and thank you again, Mr. Chairman, for having called the hearing.

Mr. JOHNSON. Without objection, that will be done, Mr. Coble.

I thank the gentleman for his statement.

[The prepared statement of Mr. Coble follows:]

PREPARED STATEMENT OF THE HONORABLE HOWARD COBLE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF NORTH CAROLINA, AND RANKING MEMBER, SUBCOMMITTEE ON COURTS AND COMPETITION POLICY

HEARING STATEMENT OF THE HONORABLE HOWARD COBLE SUBCOMMITTEE ON COURTS AND COMPETITION POLICY "BIOLOGICS AND BIOSIMILARS: BALANCING INCENTIVES FOR INNOVATORS" JULY 14, 2009

Thank you Mr. Chairman. I appreciate your calling this hearing today, which addresses an important healthcare issue and directly affects subject matter that is part of the Judiciary Committee's jurisdiction.

The Hatch-Waxman Act, which is almost a quarter-century old, gave birth to the generic chemical drug industry. By most accounts, it has worked well by balancing the interests of brand manufacturers, generic companies, and patients. It has generated greater price competition in the pharmaceutical industry without destroying the incentive for brands to conduct further research and roll-out new products that benefit patients worldwide.

In recent years, legislators and other healthcare experts have contemplated the creation of a similar legislative pathway for a "generic" biologics industry. This discussion not only resurrects some of the same issues confronting Congress during consideration of Hatch-Waxman, it also invites debate over the wisdom of using Hatch-Waxman as an appropriate template for biosimilars.

Mr. Chairman, law school was created for non-scientists such as yours truly. And while I am no expert in the fields of biology, chemistry, or recombinant DNA, I understand the basic difference between chemical pharmaceuticals and biologics. Chemical drugs are usually produced in pill form. They are chemically-synthesized and comprised of small molecules. Compared to biologics, chemical pharmaceuticals are far easier to manufacture and replicate.

Biologics are made from living organisms. They are normally composed of protein, and are increasingly a part of recombinant DNA research and production. Their characteristic properties include a high molecular weight, varying levels of hard-to-remove biological impurities, and a high degree of sensitivity to environmental conditions. The manufacturing process is therefore critical to the final product.

This complexity means one cannot guarantee that reproduction of a biological drug results in an exact duplicate. This isn't the case for a chemical pharmaceutical regulated under Hatch-Waxman, since it is chemically identical to the innovator drug. That's why the term "generic" biologic is technically inaccurate; "biosimilar" or "follow-on biologic" is preferred.

In our quest to develop a legislative pathway for biosimilars, we must keep these differences in mind. While the Judiciary Committee's jurisdiction does not include public health and related safety issues, all Members – whatever their Committee assignments – cannot disregard the importance of protecting patients. Any bill we end up supporting cannot sacrifice public safety on the altar of potential cost savings.

Nor can we disregard the importance of creating and maintaining appropriate incentives for innovator companies to do their jobs. As much as it costs a chemical pharmaceutical company to bring a state-of-the-art drug to market – about $800 million, give or take – it costs even more for a biotech firm to do the same – in excess of a billion dollars.

Our Committee retains jurisdiction over the Patent Act, which provides the greatest incentive available for pharmaceutical companies to raise capital, immerse themselves in R&D, and produce drugs – chemical and biological – that enable patients to enjoy longer and healthier lives. It is imperative that any legislation creating a biosimilar pathway contain reasonable patent and exclusivity protections. Without these incentives, the core research and development won't get done. This would cripple the industry and produce an even worse outcome for patients awaiting the next generation of biological therapeutics.

That concludes my statement, Mr. Chairman. We have a balanced and talented roster of witnesses who will add to our understanding of this complex subject. I look forward to participating, and thank you again for calling the hearing.

###

Mr. JOHNSON. Without objection, other Members' opening statements as well will be included in the record.

I am now pleased to introduce the witness for the first panel of today's hearing. Our first panel will feature Congresswoman Anna Eshoo.

Representative Eshoo, you are the top dog on this panel, there is no question about it.

Ms. ESHOO. Wait until I tell my children.

Mr. JOHNSON. You may want to put this in the new book that you are coming out with also.

Representative Eshoo has served in Congress since 1993 and represents California's 14th Congressional District, which includes large portions of Silicon Valley. She serves on the House Energy and Commerce Committee and on the House Permanent Select Committee on Intelligence. In addition, Representative Eshoo co-chairs the Congressional High-Tech Caucus and the House Medical Technology Caucus and serves as Vice Chair of the 21st Century Health Care Caucus.

Representative Eshoo, please proceed with your testimony.

TESTIMONY OF THE HONORABLE ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Ms. ESHOO. Good afternoon, Mr. Chairman, and thank you very much for allowing me to be here today to give testimony on the issue of biosimilars before this distinguished Subcommittee.

Ranking Member, Mr. Coble, a good and long-time friend, to my friends Congressman Gonzales and Congressman Watt, thank you for being here.

This is a very important, yet complex, discussion, to develop a regulatory pathway for biosimilars that, as Mr. Coble and others have said, protects patients—protects patients, that must be our number one goal—while balancing incentives for innovation.

The field of biotechnology is the future of medicine. We are just beginning to scratch the service of the potential to harness the extraordinary power of biology and the astounding natural processes which occur in the human body, in animals, and in other living organisms to advance breakthrough medical discoveries and treatments.

This vital future, in my view and I am sure yours, must advance. But the cost of biologic treatments are very expensive, and I think the time has come to develop a pathway, as the Congress did many years ago and was mentioned by the Ranking Member, to develop a pathway for biosimilar products in our country the way we did for pharmaceutical compounds.

Now, what exactly do I mean when I say develop a pathway for biosimilars? In 1984, the Drug Price Competition and Patent Term Restoration Act, better known as the Hatch-Waxman Act, ushered in a new era of competition and cheaper drugs for traditional pharmaceuticals, called compounds. It is now appropriate for us to create a pathway for follow-on versions of biologics.

But biologics and traditional drugs are fundamentally different, and they require different legal and scientific frameworks. First,

we need to understand the differences between biologics and traditional drugs.

Many of us take a prescription or an over-the-counter drug frequently. Each time we reach for a pill, we expect the same safety and efficacy, whether we are using a brand name or a generic drug.

Small molecule chemical compounds of traditional drugs are ideal for replication as generics. These products have well-defined structures that can be thoroughly characterized and copied, and generic drugs are chemically identical, chemically identical, to the brand name products they copy. Doctors and patients can expect the generics will have the same properties, the same efficacy and the same safety characteristics as the product that they copied.

Biological products are fundamentally different. A biologic is a large complex molecule which is grown in living cells, in living systems, such as a microorganism, a plant, or an animal cell. The resulting protein is unique to the cell lines and the specific processes that are used to produce it, and even slight differences, even the slightest differences, in the manufacturing of a biologic can alter its nature. And that will have an effect on the patient.

As a result, biologics are difficult and sometimes impossible to characterize, and laboratory analysis of the finished product is insufficient to ensure its safety and efficacy.

I brought a chart. They say a picture is worth a thousand words. You see on the stand here the chart. These are both breast cancer treatments. The top is Tamoxifen. That is a small-molecule compound. You can see its simplicity. The picture says it all.

Below it is Herceptin, and that is a biologic. Look at the complexity of that biologic.

Even if a biosimilar is proven to be safe and effective, it will likely still have different properties than the original innovative product. There may be differences in dosing, different side effects or safety profiles, and differences in effectiveness for certain diseases or for different patient groups.

Biologics are expensive, and they are risky to develop. A recently released study sponsored by the National Venture Capital Association analyzed the relative cost for investors in biotechnology and found that the cost of capital for startup biotech companies is more than double the costs that other companies must pay. These costs stem from long developmental timelines of typically 10 years or more and extraordinary levels of risk.

Fewer than 1 percent of biologics make it to the market. Imagine that. Fewer than 1 percent. And the large amounts of capital required to support this development are at the other end of the scale.

So, to preserve the existing incentives for investment and innovation, the Pathway for Biosimilars Act provides a data-exclusivity period equivalent to patent protections for small molecules. The Congressional Budget Office has determined that 11.5 years is the average length of time that drugs are marketed under patent. In other words, innovative drugs and biologics typically stay on the market for about 12 years before facing competition. My legislation maintains this level of protection for biologics.

Now, today innovators are assured that the costly clinical trial results and data that they develop during their approval process

cannot be used by competitors to secure approval and enter the market even if their patents do not prevent entry. In effect, innovators today have infinite data protection, which allows for competition but doesn't permit free-riding on their data.

I am proposing to allow competitors access to their data and a shortcut into the market, but we preserve through the legislation the existing incentives for innovators by maintaining a 12-year period of exclusivity of concurrent data protection as a backstop to existing patent protections.

In order to protect the rights of all parties and ensure that all patent disputes involving a biosimilar are resolved before, and I emphasis the word before, the expiration of the data-exclusivity period, H.R. 1548 also establishes a simple, streamlined patent resolution process.

This process would take place within a short window of time, roughly 6 to 8 months after the biosimilar application has been filed with the FDA. It will help ensure that litigation surrounding relevant patents will be resolved expeditiously and prior to the launch of the biosimilar product, providing certainty to the applicant, the reference product manufacturer, and the public at large.

Unlike any other proposal, our legislation also preserves the ability of third-party patent holders, such as universities and medical centers, to defend their patents.

Once a biosimilar application is accepted by the FDA, the agency will publish a notice identifying the reference product and a designated agent for the biosimilar applicant. After an exchange of information to identify the relevant patents at issue, the applicant can decide to challenge any patents' validity or applicability. All information exchanged as part of this procedure will be maintained in strict confidence and used solely for the purpose of identifying patents relevant to the biosimilar product. The patent owner will then have 2 months to decide whether to enforce the patent, and if the patent owner's case is successful in court, the final approval of the application will be deferred until the patent expires.

So this legislation I think sets forth a straightforward, scientifically-based process for an expedited approval of new biologics based on innovative products already on the market, with patient safety coming first. This new pathway will promote competition and lower prices and, most importantly again, protect patients and give them the safe and the effective treatments and I might say the hope that this represents to really conquer the most dreaded diseases that still plague humankind, and all through the scrutiny and testing by the FDA.

The legislation enjoys today 130 bipartisan cosponsors, many on this Committee, the House Judiciary Committee, and it is known as the Kennedy Bill in the Senate. Last evening, the Health Subcommittee in the Senate voted the bill out 16-7, which I think is really quite a victory for the legislation. After all, it is complicated and enormously complex, as well as enormously important.

I also want to note that the bill is endorsed by the Association of American Universities, the National Venture Capital Association, the Biotechnology Industry Organization, the Governors of four States, and a wide array of patient and industry groups.

Mr. Chairman and distinguished Members of the Subcommittee, I appreciate being welcomed here today. It is an honor to testify before my House colleagues.

I thank you, and I stand willing to answer questions, should you have any.

[The prepared statement of Ms. Eshoo follows:]

PREPARED STATEMENT OF THE HONORABLE ANNA G. ESHOO, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Statement of Congresswoman Anna G. Eshoo
House Committee on the Judiciary
Subcommittee on Courts and Competition Policy
Hearing on "Biologics and Biosimilars: Balancing Incentives for Innovation
July 14, 2009

Thank you Mr. Chairman. I'm pleased to be here today to discuss this important issue – developing a regulatory pathway for biosimilars that protects patients while balancing incentives for innovation.

The field of biotechnology is the future of medicine – we're just beginning to scratch the surface of the potential to harness the extraordinary power of biology and the astounding natural processes which occur in the human body, in animals, and in other living organisms to advance breakthrough medical discoveries and treatments.

This vital future must advance, but the costs of biologic treatments are very high and I believe the time has come to develop a pathway for biosimilar products in our country.

What, exactly, do I mean when I say "develop a pathway" for biosimilars?

In 1984 the *Drug Price Competition and Patent Term Restoration Act*, otherwise known as 'Hatch-Waxman,' ushered in a new era of competition and cheaper drugs for traditional pharmaceuticals – compounds.

It's now appropriate to create a pathway for follow-on versions of biologics. However, biologics and traditional drugs are fundamentally different and require different legal and scientific frameworks.

First, we need to understand the differences between biologics and traditional drugs.

Many of us take a prescription or over-the-counter drug frequently. Each time we reach for a pill, we expect the same safety and effectiveness, whether using a brand name or generic drug.

Small-molecule chemical compounds of traditional drugs are ideal for replication as generics. These products have well-defined structures that can be thoroughly characterized and copied, and generic drugs are chemically identical to the reference products they copy. Doctors and patients can expect that generics will have the same properties, the same efficacy, and the same safety characteristics as the innovative product they copy.

Biological products are fundamentally different. A biologic is a large, complex molecule, which is 'grown' in living systems such as a microorganism, a plant or animal cell. The resulting protein is unique to the cell lines and the specific process used to produce it, and even slight differences in the manufacturing of a biologic can alter its nature. As a result,

biologics are difficult, sometimes impossible to characterize, and laboratory analysis of the finished product is insufficient to ensure its safety and efficacy. *[SEE DISPLAY]*

Even if a biosimilar is proven to be safe and effective, it will likely still have different properties than the original innovative product. There may be differences in dosing, different side effects or safety profiles, and differences in effectiveness for certain diseases or patient groups.

Biologics are expensive and risky to develop. A recently released study sponsored by the National Venture Capital Association analyzed the relative costs for investors in biotechnology and found that the "cost of capital" for start-up biotech companies is more than double the costs that other companies must pay. These costs stem from long developmental timelines of typically 10 years or more, extraordinary levels of risk (fewer than 1% of biologics make it to market), and the large amounts of capital required to support development.

To preserve existing incentives for investment and innovation the *Pathway for Biosimilars Act* provides a data exclusivity period equivalent to patent protections for small molecules. The Congressional Budget Office has determined that 11.5 years is the average length of time that drugs are marketed under patent. In other words, innovative drugs and biologics typically stay on the market for about 12 years before facing competition. My legislation maintains this level of protection for biologics.

Today innovators are assured that the costly clinical trial results and data that they develop during their approval process cannot be used by competitors to secure approval and enter the market, even if their patents do not prevent entry. In effect innovators now have "infinite" data protection, which allows for competition but doesn't permit "free riding" on their data.

I'm proposing to allow competitors access to their data and a shortcut into the market, but also preserving the existing incentives for innovators by maintaining a 12-year period of concurrent data protection as a "backstop" to existing patent protections.

In order to protect the rights of all parties and ensure that all patent disputes involving a biosimilar are resolved before the expiration of the data exclusivity period, H.R. 1548 also establishes a simple, streamlined patent resolution process.

This process would take place within a short window of time – roughly 6-8 months after the biosimilar application has been filed with the FDA. It will help ensure that litigation surrounding relevant patents will be resolved expeditiously and prior to the launch of the biosimilar product, providing certainty to the applicant, the reference product manufacturer, and the public at large.

Unlike any other proposal, our legislation also preserves the ability of third-party patent holders such as universities and medical centers to defend their patents.

Once a biosimilar application is accepted by the FDA, the agency will publish a notice identifying the reference product and a designated agent for the biosimilar applicant. After an exchange of information to identify the relevant patents at issue, the applicant can decide to challenge any patent's validity or applicability. All information exchanged as part of this procedure must be maintained in strict confidence and used solely for the purpose of identifying patents relevant to the biosimilar product.

The patent owner will then have two months to decide whether to enforce the patent. If the patent owner's case is successful in court, the final approval of the application will be deferred until the patent expires.

The *Pathway for Biosimilars Act* sets forth a straightforward, scientifically based process for expedited approval of new biologics based on innovative products already on the market. This new biosimilars approval pathway will promote competition and lower prices, but also ensure that patients are given safe and effective treatments that have been subjected to thorough scrutiny and testing by the FDA.

I'm pleased that Congressmen Inslee, Barton and I have been joined by a diverse group of 125 bipartisan cosponsors in the House.

I also want to note that my bill is the only legislation endorsed by the Association of American Universities, the National Venture Capital Association, the Biotechnology Industry Organization, the governors of 4 states, and a wide array of patient and industry groups.

This broad support is extremely encouraging, and I look forward to working finally addressing this critical issue in the 111th Congress.

Thank you again for inviting me to testify today.

Mr. JOHNSON. Thank you, Madam Congresswoman. It is our pleasure to host you today.

Without objection, your written statement will be placed into the record.

I now call for the second panel to take their seats. Thank you.

I might add here also that Representative Waxman has introduced a similar bill, and he was offered the opportunity to come

EXHIBIT 26

REDACTED IN ITS ENTIRETY

EXHIBIT 27


Roche

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2018 results

London, 31 January 2019

Roche

This presentation contains certain forward-looking statements. These forward-looking statements may be identified by words such as 'believes', 'expects', 'anticipates', 'projects', 'intends', 'should', 'seeks', 'estimates', 'future' or similar expressions or by discussion of, among other things, strategy, goals, plans or intentions. Various factors may cause actual results to differ materially in the future from those reflected in forward-looking statements contained in this presentation, among others:

1 pricing and product initiatives of competitors;
2 legislative and regulatory developments and economic conditions;
3 delay or inability in obtaining regulatory approvals or bringing products to market;
4 fluctuations in currency exchange rates and general financial market conditions;
5 uncertainties in the discovery, development or marketing of new products or new uses of existing products, including without limitation negative results of clinical trials or research projects, unexpected side-effects of pipeline or marketed products;
6 increased government pricing pressures;
7 interruptions in production;
8 loss of or inability to obtain adequate protection for intellectual property rights;
9 litigation;
10 loss of key executives or other employees; and
11 adverse publicity and news coverage.

Any statements regarding earnings per share growth is not a profit forecast and should not be interpreted to mean that Roche's earnings or earnings per share for this year or any subsequent period will necessarily match or exceed the historical published earnings or earnings per share of Roche.

For marketed products discussed in this presentation, please see full prescribing information on our website www.roche.com

Roche

Group

Severin Schwan
Chief Executive Officer

Roche

2018 performance

Outlook

2018: Targets fully achieved

Targets for 2018		2018	
Group sales growth[1]	Mid-single digit (raised at HY)	**+7%**	✓
Core EPS growth[1]	Broadly in line with sales growth, excl. US tax reform benefit Mid teens incl. US tax reform (raised at HY)	**+8%** **+19%**	✓
Dividend outlook	Further increase dividend in Swiss francs[2]	**CHF 8.70**	✓

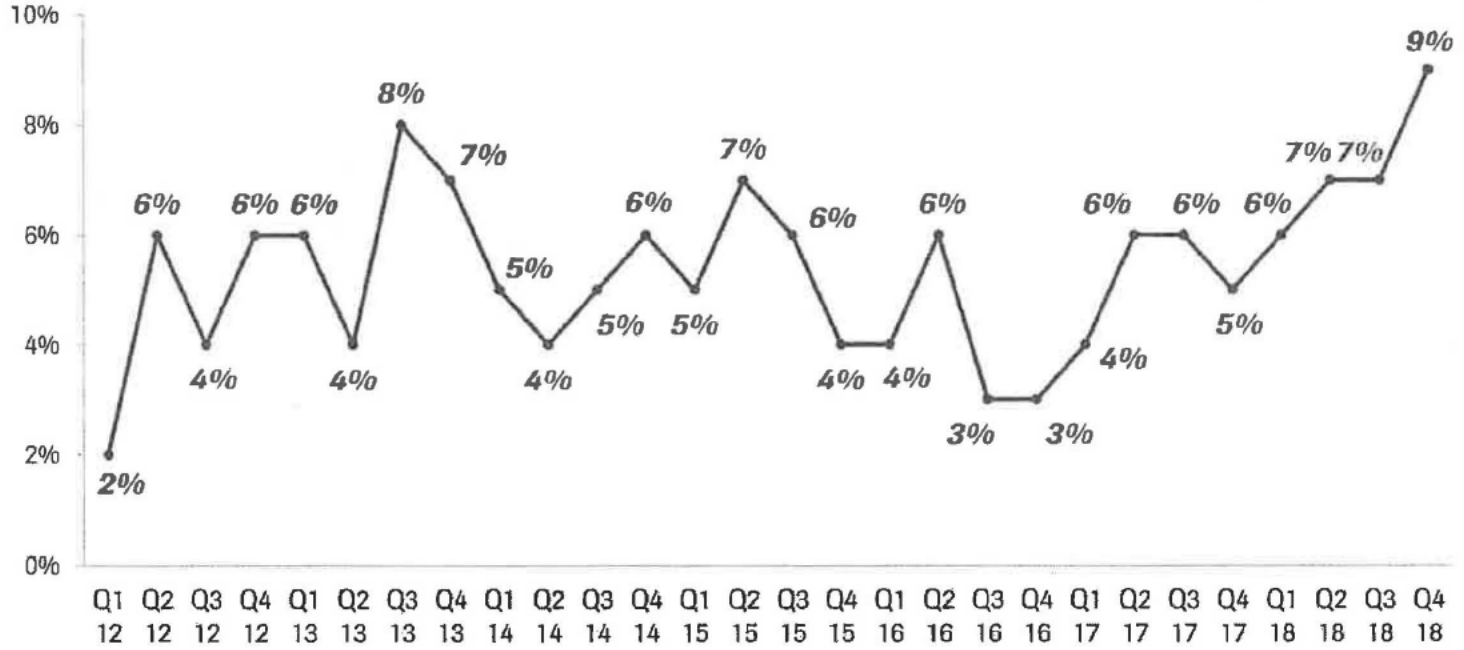
[1] At constant exchange rates (CER); [2] 2018 dividend as proposed by the Board of Directors

2018: Strong sales growth in both divisions

	2018 CHFbn	2017 CHFbn	Change in % CHF	CER
Pharmaceuticals Division	**44.0**	41.2	**7**	**7**
Diagnostics Division	**12.9**	12.1	**7**	**7**
Roche Group	**56.8**	53.3	**7**	**7**

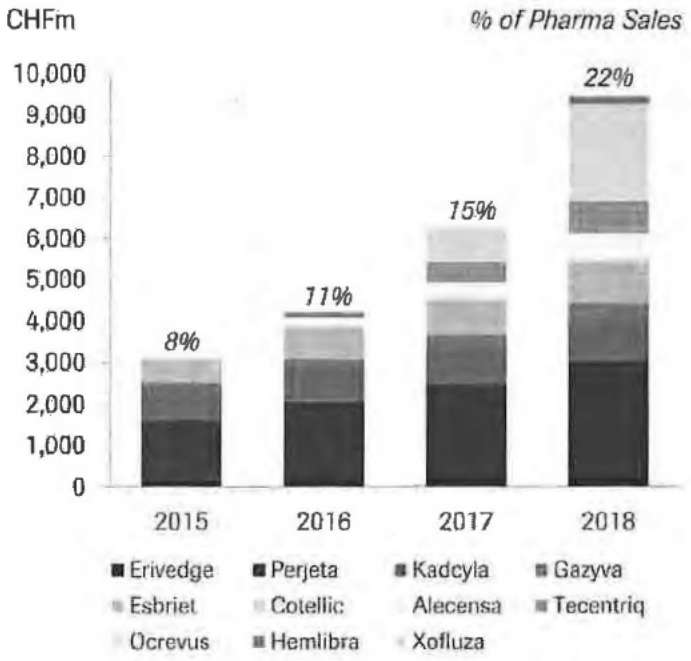
CER=Constant Exchange Rates

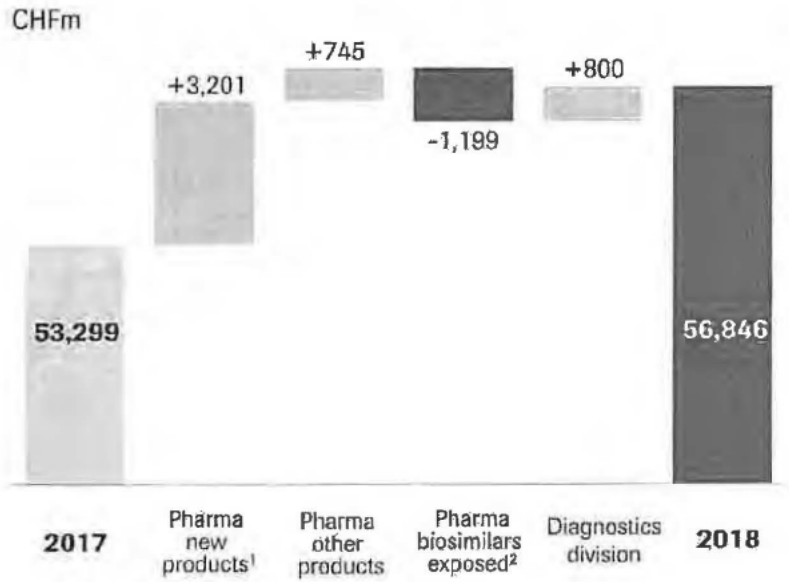
2018: Sales growth for the seventh consecutive year



All growth rates at Constant Exchange Rates (CER)

New products with strong momentum offsetting biosimilars impact





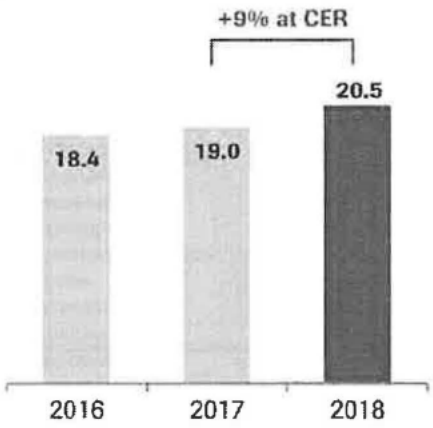
All absolute values are presented in CHFm reported; [1] Erivedge, Perjeta, Kadcyla, Gazyva, Esbriet, Cotellic, Alecensa, Tecentriq, Ocrevus, Hemlibra, and Xofluza; [2] MabThera and Herceptin in Europe and Japan

2018: Strong Core results, significant operating free cash flow

Core operating profit

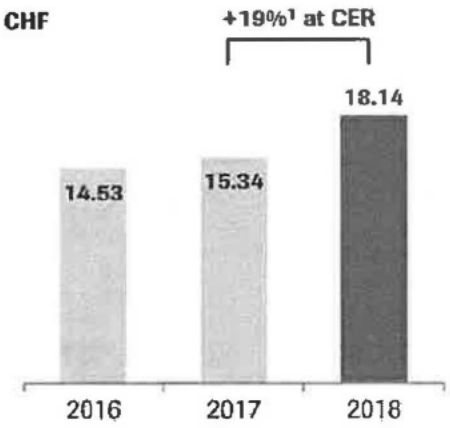
% of sales: 36.4% 35.7% 36.1%

CHFbn



Core EPS

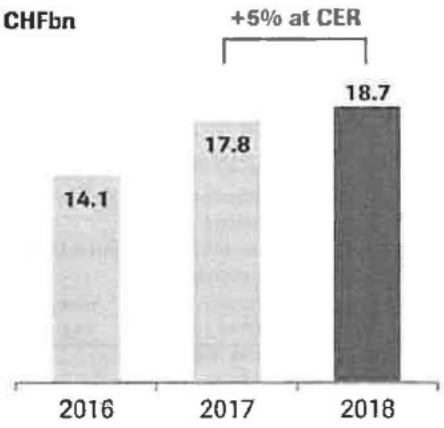
CHF



Operating free cash flow

27.9% 33.4% 33.0%

CHFbn



CER=Constant Exchange Rates; ¹+8% at CER excl. US tax reform

Roche significantly advancing patient care

BTD's and BDD's reflecting the quality of our research

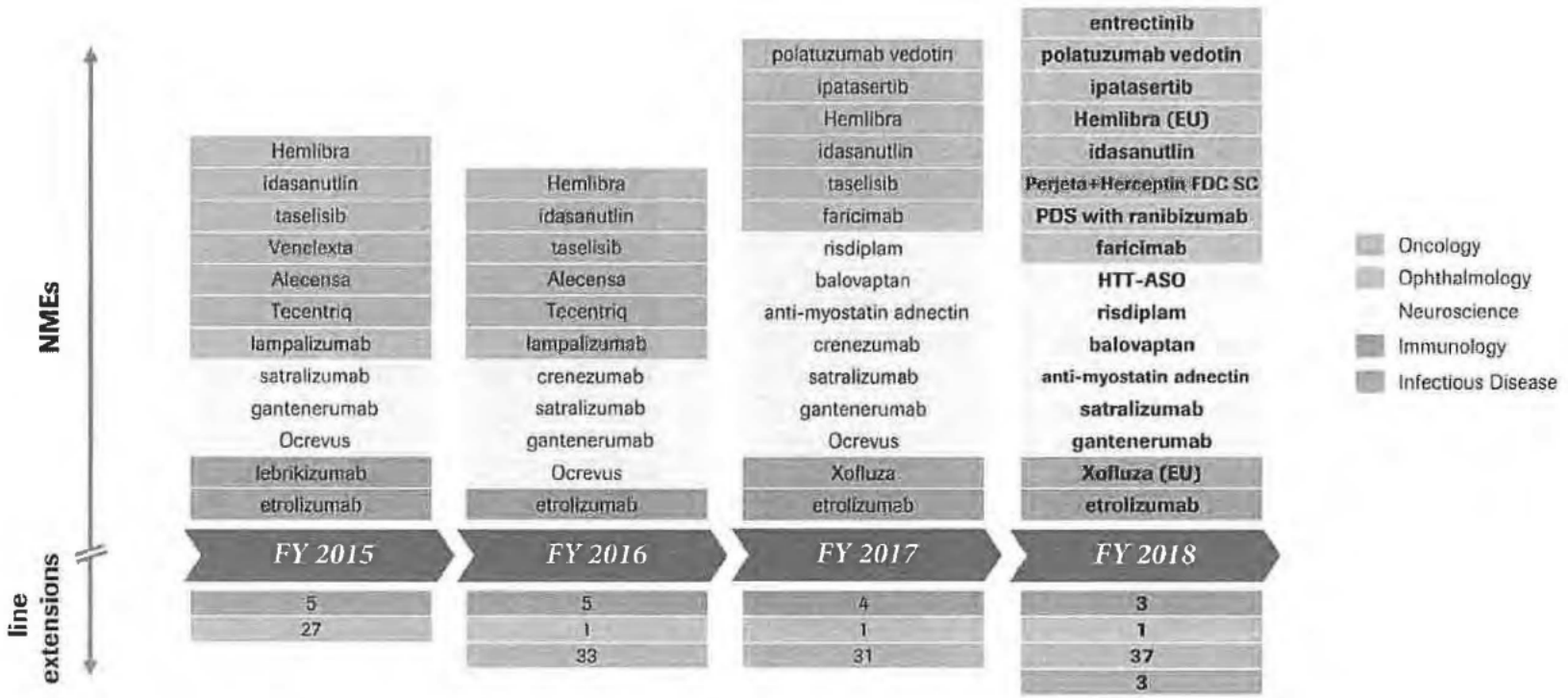
25 *Breakthrough Therapy Designations (BTD)*

Year	Molecule	Indication
2019	**Kadcyla**	Adjuvant HER2+ BC
2018	**satralizumab**	NMOSD
	Xolair	Food allergies
	Tecentriq + Avastin	HCC
	Hemlibra	Hemophilia A non-inhibitors
	entrectinib	NTRK+ solid tumors
	balovaptan	Autism spectrum disorders
2017	**polatuzumab vedotin + BR**	R/R DLBCL
	Venclexta + LDAC	1L unfit AML
	Zelboraf	BRAF-mutated ECD
	Rituxan	Pemphigus vulgaris
2016	**Actemra**	Giant cell arteritis
	Alecensa	1L ALK+ NSCLC
	Ocrevus	PPMS
	Venclexta + HMA	1L unfit AML
	Venclexta + Rituxan	R/R CLL
2015	**Actemra**	Systemic sclerosis
	Tecentriq	NSCLC
	Venclexta	R/R CLL 17p del
	Hemlibra	Hemophilia A inhibitors
2014	**Esbriet**	IPF
	Lucentis	Diabetic retinopathy
	Tecentriq	Bladder
2013	**Alecensa**	2L ALK+ NSCLC
	Gazyva	1L CLL

7 *Breakthrough Device Designations (BDD)*

Year	Device	Intended use
2018	**Elecsys β-Amyloid + p-Tau**	AD: PET concordance
	Cerebro Spinal Fluid assays	AD: Progression
	sFlt + PLGF	Preeclampsia: rule-out within 1w
	FACT CDx (liquid biopsy assay)	70 oncogenes + MSI + bTMB
	cobas EBV	EBV in transplant patients
	cobas BKV	BKV in transplant patients
	CoaguChek Direct-X	Patients on Factor Xa

2018: Record number of NMEs at pivotal stage



NME=new molecular entities; risdiplam (SMN2 splicer); FDC=Fixed dose combination; SC=Subcutaneous; PDS=Port delivery system; For details on the indications and line extensions please consult the pipeline appendix

Replace and extend the business: Excellent progress in 2018

Roche

Replace/extend existing businesses		Entering new franchises
MabThera/Rituxan	Gazyva, Venclexta, polatuzumab vedotin, mosunetuzumab, aCD20/CD3 TCB	**MS:** Ocrevus satralizumab
Herceptin	Perjeta, Kadcyla, Herceptin + Perjeta SC	**Hemophilia A:** Hemlibra
Avastin	Tecentriq, Alecensa, entrectinib	
Lucentis	faricimab Port delivery system (PDS)	**CNS:** SMA, Autism, Huntington's, Alzheimer's, NMOSD
Tamiflu	Xofluza	

Achievements 2018
Approvals and major read-outs

Entering new franchises

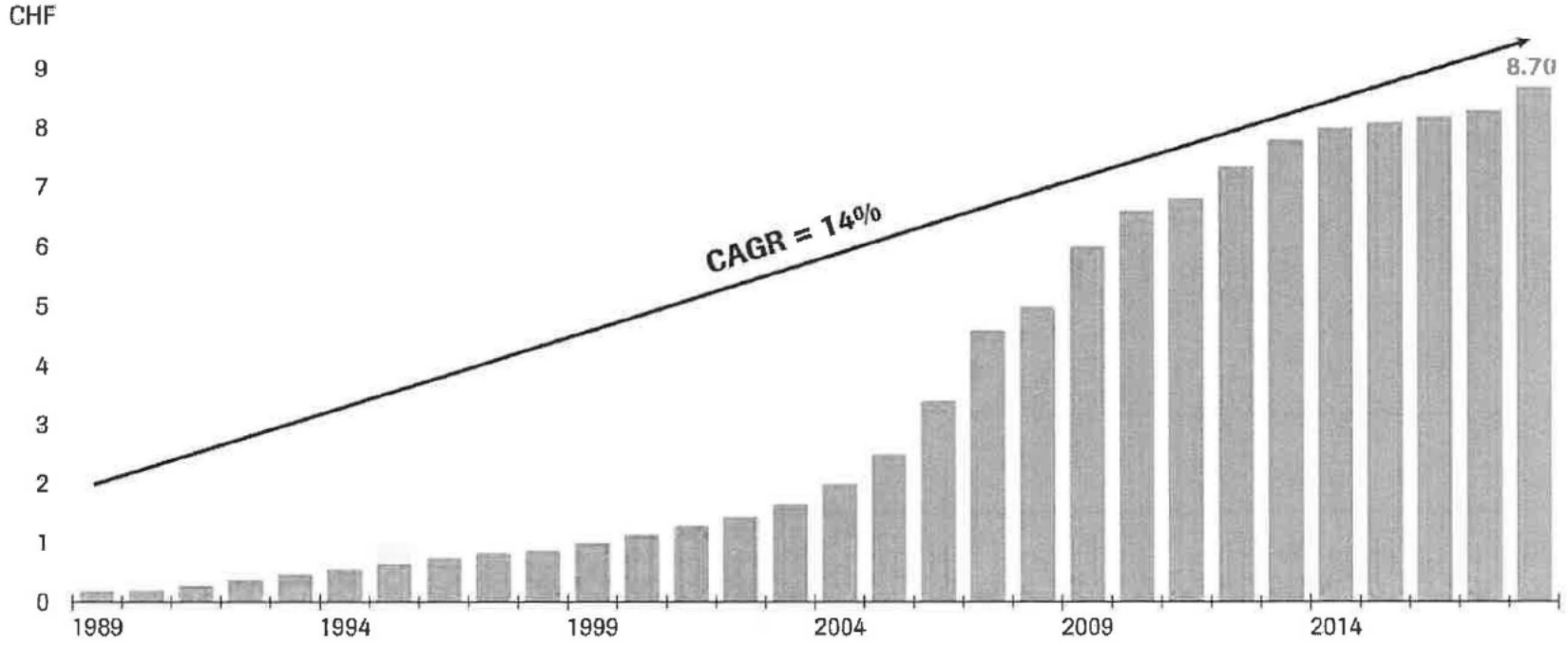
Ocrevus:	EU approval in RMS/PPMS
satralizumab:	2 positive Ph III in NMOSD
Hemlibra:	US/EU/Japan launch in Hemophilia A
Venclexta:	US approval in R/R CLL & 1L AML
risdiplam:	Positive preliminary Ph II in SMA
balovaptan:	Start of Ph III in adults with autism

Replace/extend existing businesses

Gazyva+Ven:	Positive Ph III in 1L CLL
Kadcyla:	Positive Ph III in adjuvant HER2+ BC
Tecentriq:	US approval in 1L non-sq NSCLC; US/EU filing in 1L SCLC & TNBC
entrectinib:	US/EU filing ROS1+ NSCLC & NTRK+ tumors
faricimab:	Positive Ph II in nAMD and DME
PDS:	Positive Ph II in nAMD
Xofluza:	US approval in Influenza A and B

SMA=spinal muscular atrophy; NMOSD=neuromyelitis optica spectrum disorder; RMS=relapsing MS; PPMS=primary progressive MS; R/R CLL=relapsed/refractory chronic lymphocytic leukemia; AML=acute myeloid leukemia; BC=breast cancer; NSCLC=non-small cell lung cancer; SCLC=small cell lung cancer; TNBC=triple-negative BC; nAMD=neovascular age-related macular degeneration; DME=diabetic macular edema

2018: 32nd consecutive annual dividend increase



2018 dividend as proposed by the Board of Directors; Note: For 1995, a special dividend was paid out to mark F. Hoffmann-La Roche's 100th anniversary in 1996

Outlook

2019: Roche significantly advancing patient care

Another strong year expected

3	**NME launches**	• Xofluza (baloxavir marboxil) • entrectinib in ROS1+ and NTRK+ tumors* • polatuzumab vedotin in R/R DLBCL*
7	**Major line extension launches**	• Hemlibra (non-inhibitor) in EU • Kadcyla in adj HER2+ BC • Venclexta in 1L AML and 1L CLL • Tecentriq in 1L TNBC, 1L SCLC, 1L NSCLC
2	**Major NME filings**	• satralizumab in NMOSD • risdiplam in SMA
1	**Diagnostics platform**	• Further roll-out of cobas pro integrated solutions

*filed end of 2018; NME=new molecular entities; R/R CLL=relapsed/refractory diffuse large B-cell lymphoma; AML=acute myeloid leukemia; CLL= chronic lymphocytic leukemia; TNBC=triple-negative BC; SCLC=small cell lung cancer; NSCLC=non-small cell lung cancer; NMOSD=neuromyelitis optica spectrum disorder; SMA=spinal muscular atrophy

2019 outlook

Group sales growth[1]	• Low-to mid-single digit
Core EPS growth[1]	• Broadly in line with sales
Dividend outlook	• Further increase dividend in Swiss francs

[1] At Constant Exchange Rates (CER)

Roche

Pharmaceuticals Division

Bill Anderson
CEO Roche Pharmaceuticals

2018: Pharma Division sales

Strong growth in US due to new products

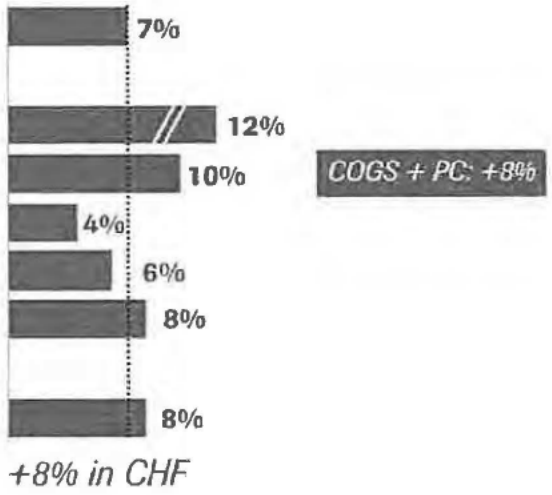
	2018 CHFm	2017 CHFm	Change in % CHF	Change in % CER
Pharmaceuticals Division	**43,967**	**41,220**	**7**	**7**
United States	23,233	20,496	13	14
Europe	8,693	9,051	-4	-7
Japan	3,701	3,713	0	-1
International	8,340	7,960	5	10

CER=Constant Exchange Rates

2018: Pharma Division
Core operating profit outgrowing sales

	2018 CHFm	2018 % sales
Sales	**43,967**	**100.0**
Royalties & other op. inc.	2,553	5.8
Cost of sales	-9,504	-21.6
M & D	-6,939	-15.8
R & D	-9,586	-21.8
G & A	-1,549	-3.5
Core operating profit	**18,942**	**43.1**

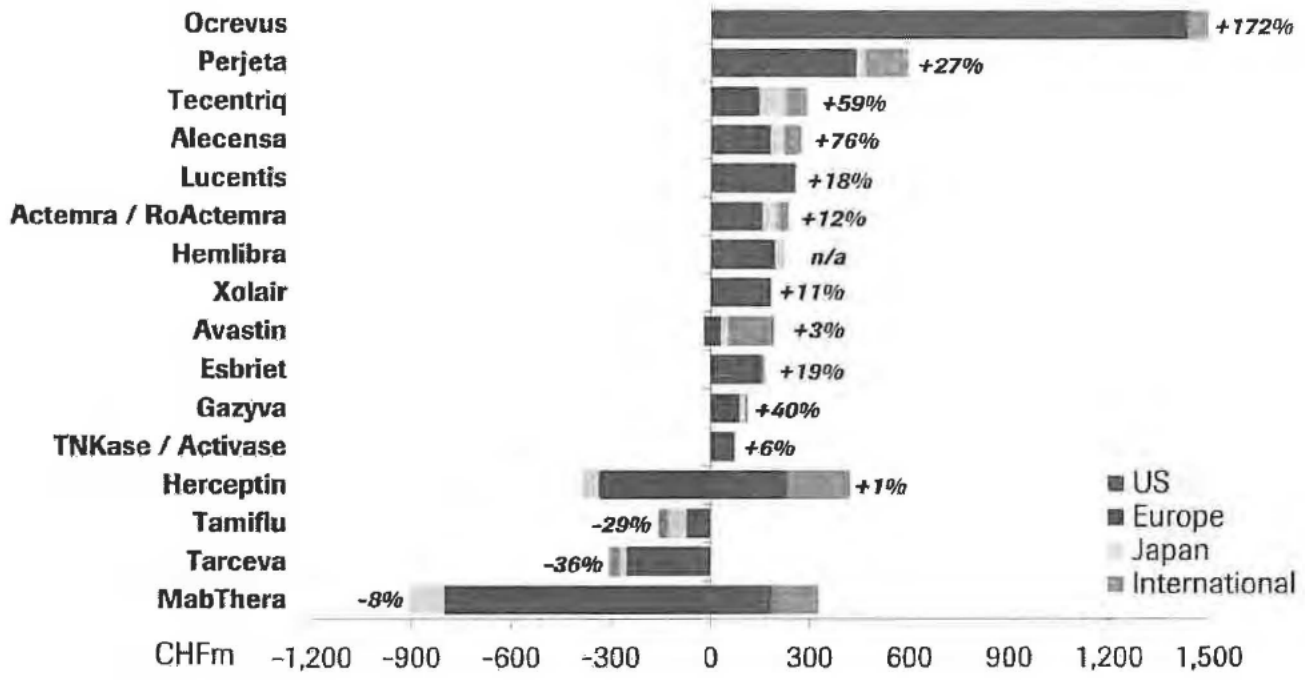
2018 vs. 2017
CER growth



CER=Constant Exchange Rates; COGS=costs of goods sold; PC=period costs

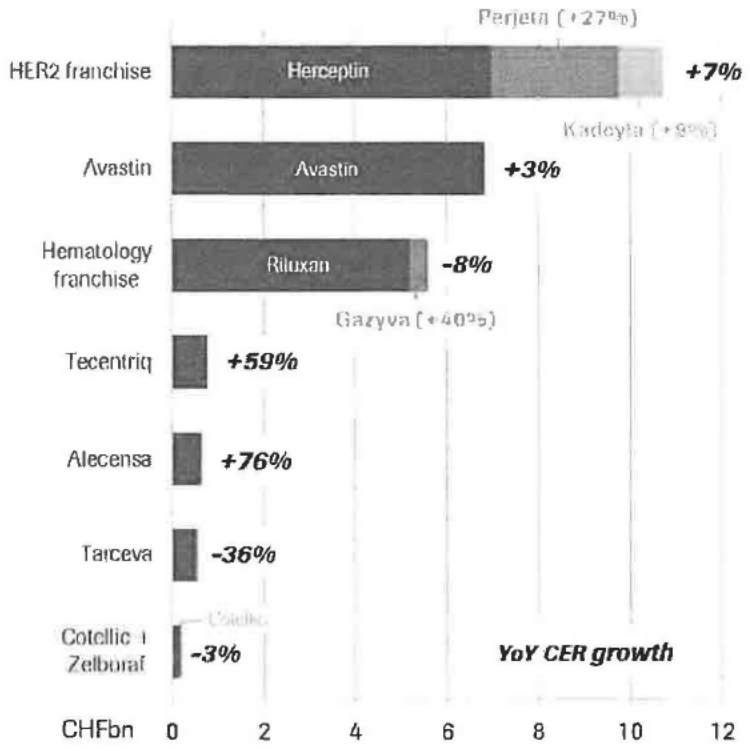
2018: Portfolio rejuvenation in full swing

Growth exclusively driven by new products



Absolute values and growth rates at Constant Exchange Rates (CER)

2018: Oncology grows +2% with new products offsetting biosimilars



Oncology Q4 update

HER2

- Perjeta: Accelerated growth driven by eBC (APHINITY)
- Herceptin: Impact from biosimilars in EU as expected

Hematology

- Venclexta*: Accelerated momentum due to strong 1L AML launch
- Gazyva: Growth remains driven by 1L FL
- MabThera/Rituxan: Biosimilar erosion rate stabilizing in EU

Tecentriq

- Sales momentum in all geographies, upcoming new launches

Alecensa

- Strong 1L launch momentum in all key markets

* **Venclexta sales of USDm 344 (+177% YoY)** are booked by partner AbbVie and therefore not included; 2018 Oncology sales: CHF 26.2bn; CER growth +2%; CER=Constant Exchange Rates; eBC=early breast cancer; AML=acute myeloid leukemia; FL=follicular lymphoma

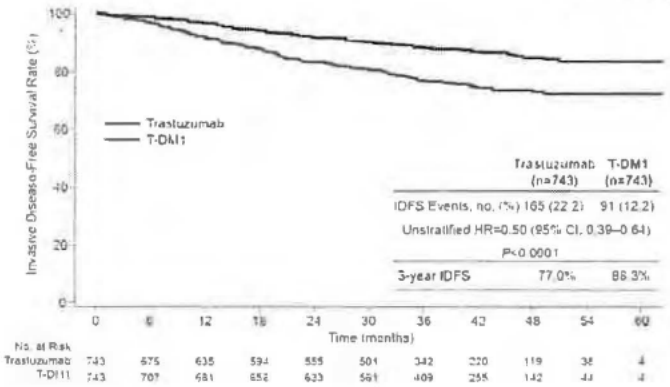
HER2 franchise

Kadcyla in adjuvant HER2+ eBC for patients with residual disease

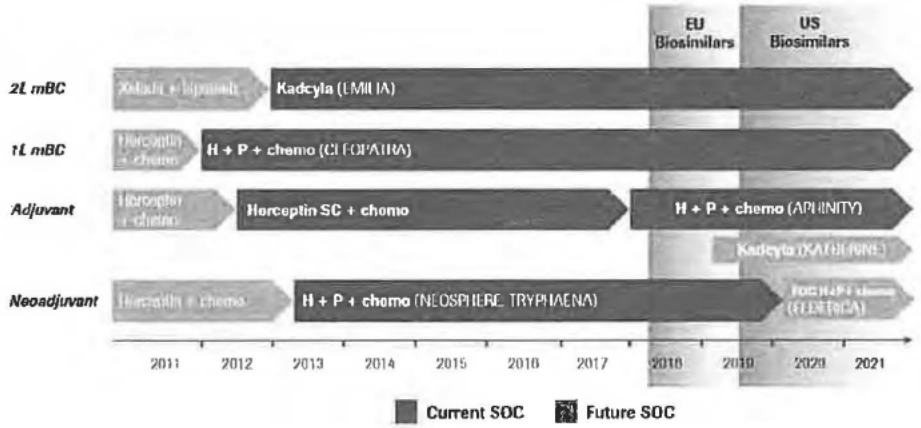
Kadcyla: Ph III (KATHERINE) results

Invasive disease free survival

FDA BTD



Standard of care (SOC) evolution



- New SOC in patients with residual invasive disease after neoadjuvant chemo and HER2 targeted therapy
- Increased use of neoadjuvant therapy in HER2-positive eBC expected
- BTD granted; US/EU filing and US approval expected in 2019

Geyer E.C. et al., SABCS 2018; eBC=early breast cancer; HR=hazard ratio; OS=overall survival; H+P=Herceptin+Perjeta; FDC=fixed dose combination; Kadcyla=trastuzumab emtansine (T-DM1)

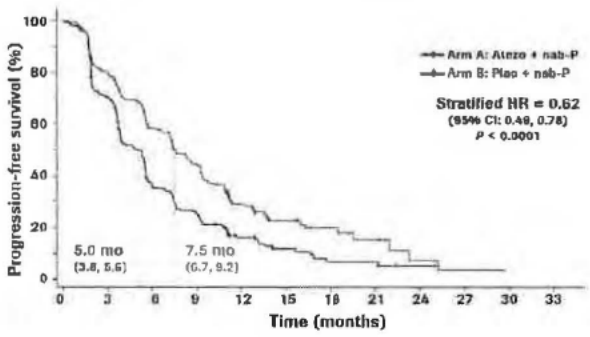
Emerging triple negative breast cancer (TNBC) franchise
Tecentriq + chemo new SOC in 1L PDL1+ patients

Roche

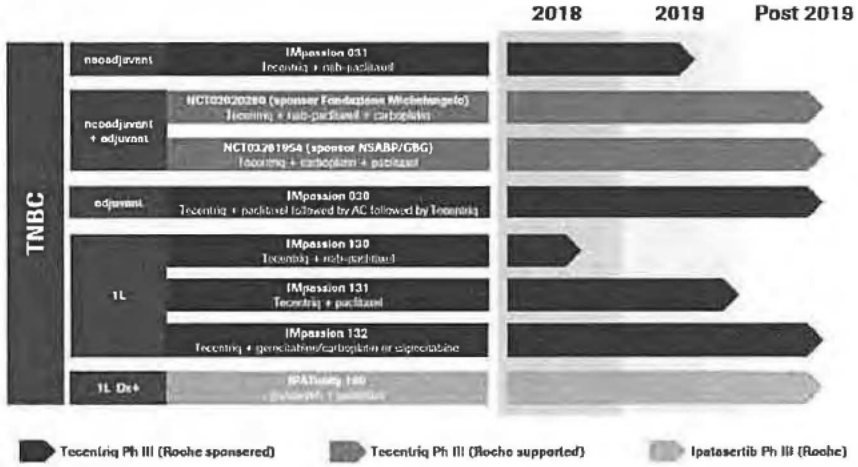
MUNICH 2018 ESMO congress

Tecentriq+nab-pac: Ph III (IMpassion130)

Progression free survival (PFS)
PDL1+ population



TNBC program covering all lines of treatment*

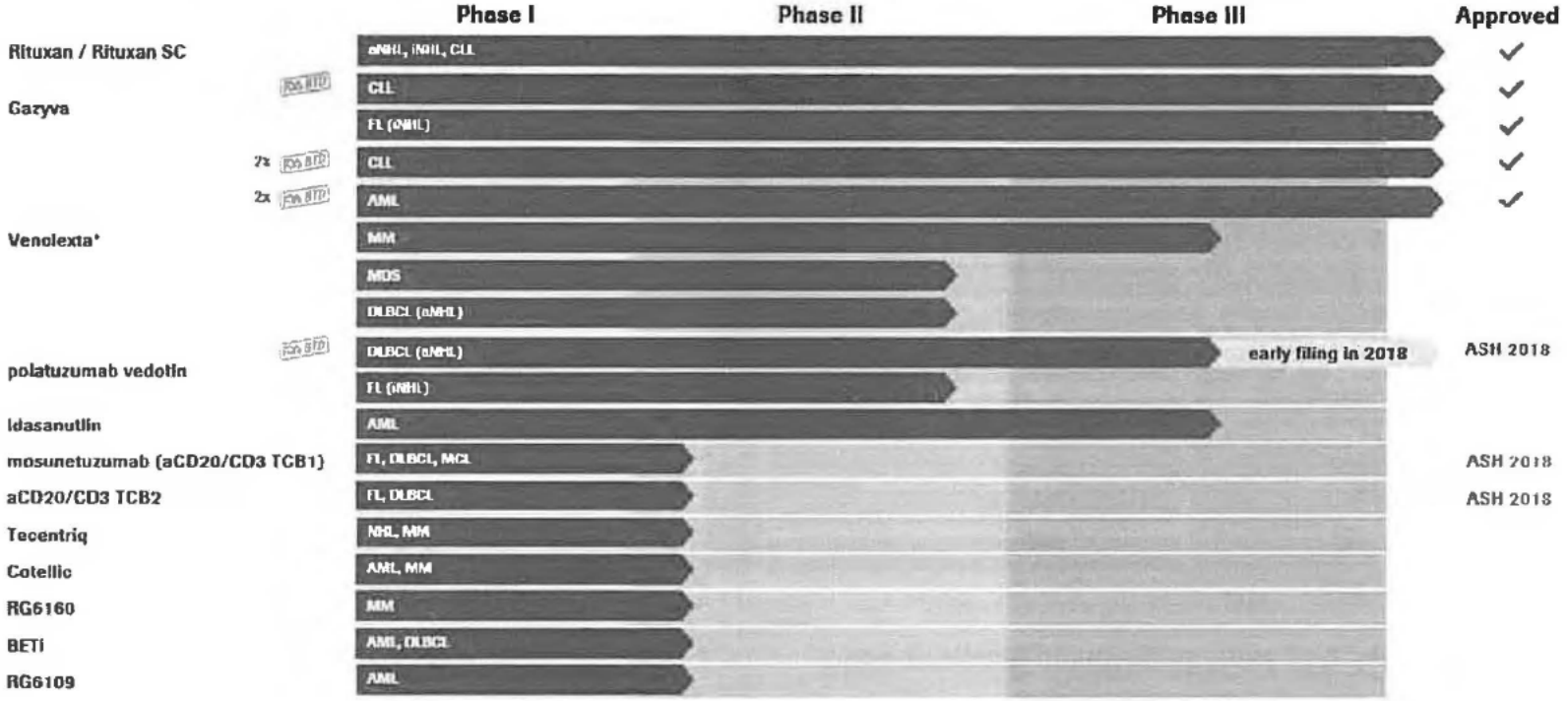


- PFS in ITT (HR=0.80) and PD-L1+ patients (HR=0.62); Interim OS with clinically meaningful improvement in PD-L1+ patients (HR=0.62) with mOS improvement from 15.5m to 25.0m
- US/EU filing completed (PDUFA March 12)

Schmid P, et al. ESMO 2018 (Data cutoff: 17 April 2018); TNBC=triple negative breast cancer; nab-pac=nab-paclitaxel (Abraxane); ITT=intent to treat; HR=hazard ratio; OS=overall survival;
*Outcome studies are event-driven: timelines may change

Hematology franchise

Broadest portfolio with 12 assets in combination trials



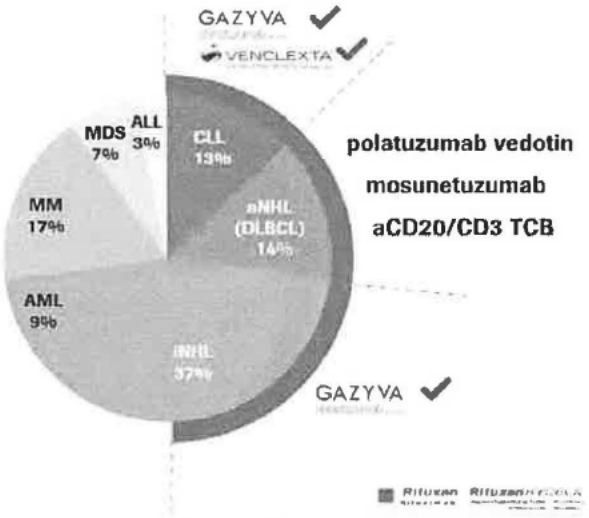
*Venclexta in collaboration with AbbVie; polatuzumab vedotin in collaboration with Seattle Genetics; Cotellic in collaboration with Exelixis; NHL=non-hodgkin's lymphoma; FL = follicular lymphoma; CLL=chronic lymphoid leukemia; MM=multiple myeloma; MDS=myelodysplastic syndrom; AML=acute myeloid leukemia; MCL=mantle cell lymphoma; DLBCL=diffuse large B cell lymphoma

Hematology franchise
Redefining the SOC and expanding into new indications

Roche

60th ASH® Annual Meeting & Exposition

Continuing to redefine the SOC in B-cell malignancies

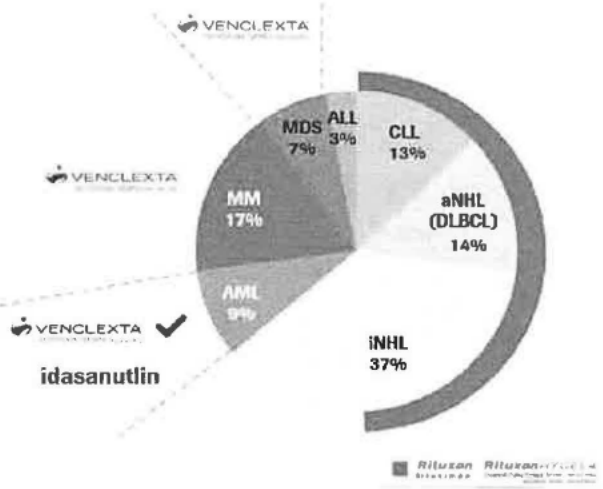


polatuzumab vedotin

mosunetuzumab

aCD20/CD3 TCB

Expanding into new indications with transformative therapies



Datamonitor: incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); SOC=standard of care; CLL=Chronic lymphoid leukemia; DLBCL=Diffuse large B-cell lymphoma; iNHL=Indolent Non-Hodgkin's lymphoma; AML=Acute myeloid leukemia; MM=Multiple myeloma; MDS=Myelodysplastic syndrome; ALL=Acute lymphoblastic leukemia; Venclexta in collaboration with AbbVie; polatuzumab vedotin in collaboration with Seattle Genetics

Hematology franchise

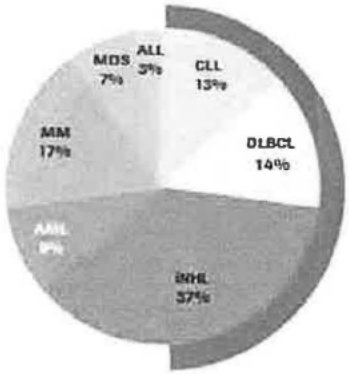
Venclexta + HMA/LDAC new SOC in 1L unfit AML

Roche

60th ASH® Annual Meeting & Exposition

FDA BTD

AML incidence rate[1]



- Incidence rate: US 19.2k; EU5 15.1k
- ~50% of 1L AML patients unfit for intense chemotherapy

PhIb/II update in 1L unfit AML

CR rates doubled compared to historical SOC

	Ven (400mg) + azacitadine	Ven (400mg) + decitabine	azacitadine (historical data)[2]
CR	44%	55%	~20%
CR+CRi	71%	74%	~28%
MRD-negative	48%	39%	N/A
mOS	16.9m	16.2m	10.4m

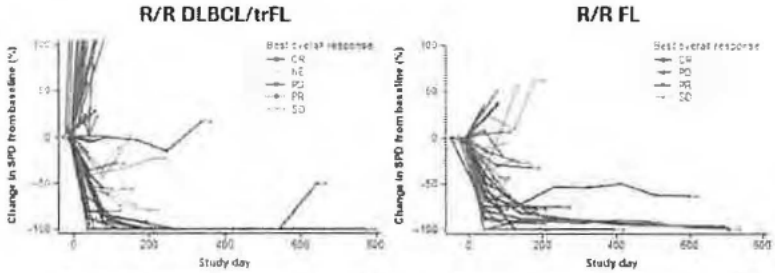
- **1L AML**: Accelerated FDA approval in 1L unfit AML achieved; Two confirmatory Ph III trials (Viale-A, Viale-C) in 1L AML ongoing
- **R/R AML**: Promising early activity of Venclexta+idasanutlin presented; Ph III (MIRROS) results of idasanutlin+chemo expected in 2019

Pollyea, *et al.*, ASH 2018; 2 Dombret H., et al., International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood.* 2016;128 (3): 291-299; [1] Datamonitor: incidence rates includes the 7 major markets (US, Japan, France, Germany, Italy, Spain, UK); SOC=standard of care; AML=acute myeloid leukemia; HMA=hypomethylating agent; LDAC=low dose aracytarabine; MRD=minimal residual disease; CR=complete response; mOS=median overall survival; Venclexta in collaboration with AbbVie

Hematology franchise

TCBs with strong efficacy and tolerable safety in NHL

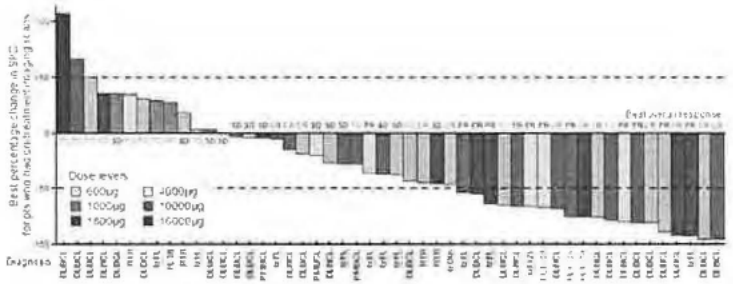
Mosunetuzumab: Ph I/Ib dose escalation



ORR 16/47 (34.0%)
CR 9/47 (19.1%)

ORR 18/26 (69.2%)
CR 10/26 (38.5%)

aCD20/CD3 TCB: Ph Ib dose escalation



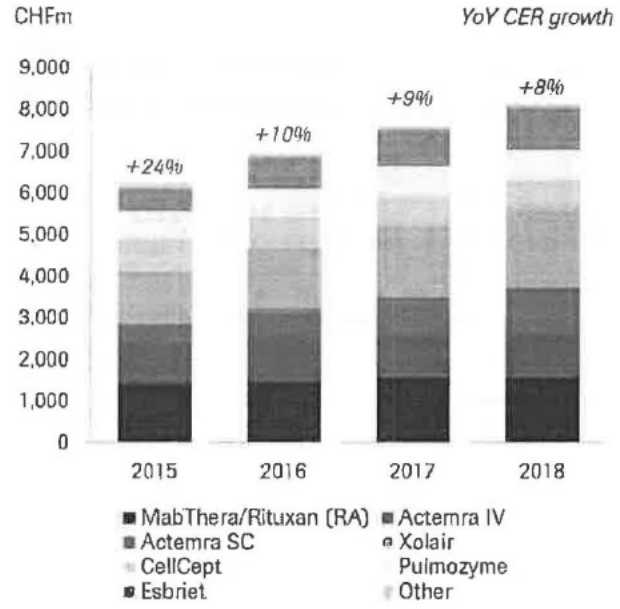
aNHL/DLBCL 10mg cohort*
ORR 9/15 (60%)
CR 5/15 (33%)

- Durable CRs as a single agent in 2L+ iNHL/aNHL
- CRs in patients refractory to R-CHOP and CAR-T
- Combination trials with Tecentriq, polatuzumab vedotin and CHOP ongoing
- Dose escalation ongoing

Budde L, et al, ASH 2018; Hutchings, M., et al, ASH 2018; CAR T cells=chimeric antigen receptor; CR=complete response; SPD=sum of the product diameters; R/R=relapsed/refractory; DLBCL=diffuse large B-cell lymphoma; FL=Follicular Lymphoma; AE=adverse event; NHL=non-Hodgkin's lymphoma; TCB=T=cell bispecific; *aNHL includes FL Grade 3B, DLBCL, trFL, PMBCL, MCL, trMZL, RS and DLBCL/MCL

Immunology franchise

Immunology sales hit CHF 8bn driven by well differentiated products



Immunology Q4 update

Esbriet

- Strong growth in mild to moderate patient segments

Actemra

- Ongoing launches in giant cell arteritis (GCA) and of pre-filled syringe in pJIA and sJIA
- US: Autoinjector approval received

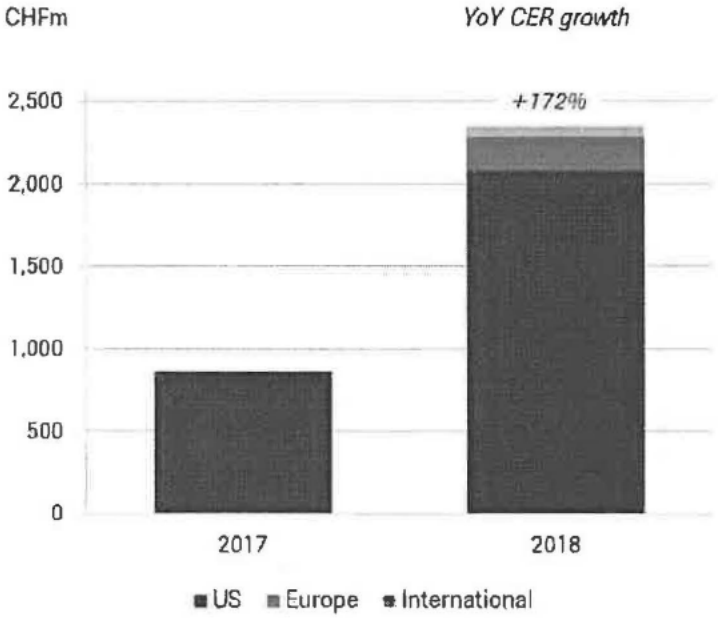
Xolair

- Growth driven by CIU, pediatric asthma and allergic asthma
- Pre-filled syringe launched; Self-administration filing ongoing

CER=Constant Exchange Rates; pJIA= polyarticular juvenile idiopathic arthritis; sJIA=systemic juvenile idiopathic arthritis; RA=rheumatoid arthritis; CIU=chronic idiopathic urticaria

Neuroscience franchise

Ocrevus with 15% total US market share after 20 months



Ocrevus Q4 update

- Strong launches in EU and International
- US driven by earlier lines, new and returning patients
- 5-Year efficacy and safety data presented at ECTRIMS
- Continue to generate new data in progressive MS (PMS) including new Phase III study using upper limb function and digital outcomes as measures of progression

Outlook 2019

- Moving into earlier lines displacing orals
- Continued launches in EU and International

CER=Constant Exchange Rates

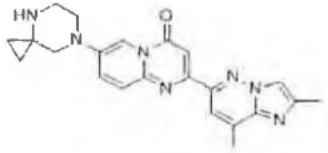
Neuroscience franchise

Risdiplam in spinal muscular atrophy (SMA) types 1/2/3

Roche

WMS World Muscle Society CONGRESS 2018

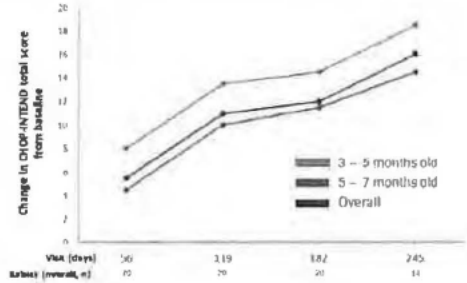
SMN2 splicing modifier



- Oral and systemically available SMN2 splicing modifier
- Durably increases SMN protein both in the CNS and in the periphery
- To date well tolerated at all doses assessed

Phase II/III (FIREFISH) Part 1 data in Type 1 SMA:

Median change from baseline in CHOP-INTEND



HINE-2 motor milestones

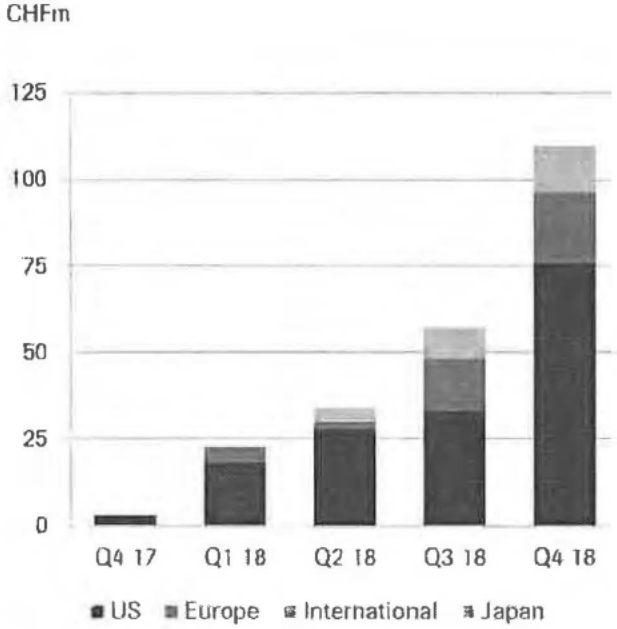
	Baseline (n=21)	8 months (n=14)
Upright head control	0%	43%
Kicking	5%	50%
Rolling	0%	29%
Stable sitting	0%	21%

- 20/21 babies (95%) were alive and without need of permanent ventilation at 10.5m, compared with 50% of babies at the same age in natural history studies
- No patients have lost the ability to swallow or reached permanent ventilation
- Among babies with 8m treatment: median change in CHOP-INTEND was 16 points and 21% achieved unassisted stable sitting
- Presymptomatic Ph III (RAINBOWFISH) in 0-6 week old babies starting in Q1 2019
- NME filing targeted in H2 2019

Baranello G. et al., WMS 2018; WMS=world muscle society; SMA=spinal muscular atrophy; CHOP-INTEND=Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (16-item 64-point motor assessment designed specifically to evaluate the motor skills of infants with SMA); HINE-2=Hammersmith Infant Neurological Examination Module 2; Risdiplam in collaboration with PTC Therapeutics and the SMA Foundation

Hemophilia A franchise

Hemlibra with strong initial uptake in non-inhibitors



Hemlibra Q4 update

- US: Strong uptake in non-inhibitors and further market share gains in inhibitors
- Germany, France, UK: Inhibitor market share gains
- Strong preference data for Hemlibra in patients previously receiving episodic (92% preference) or prophylactic factor treatment (99% preference)

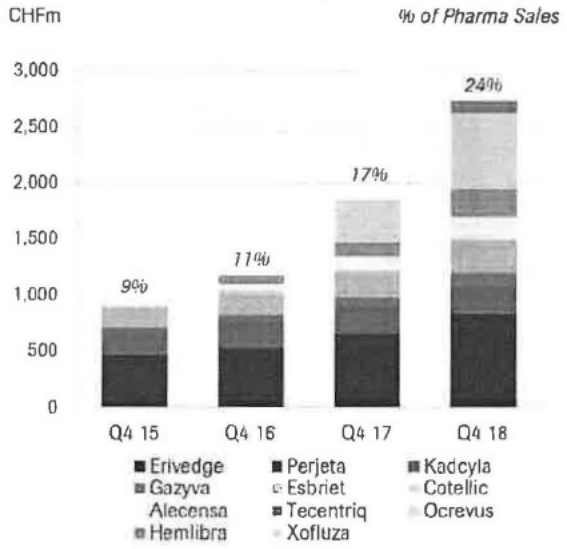
Outlook 2019

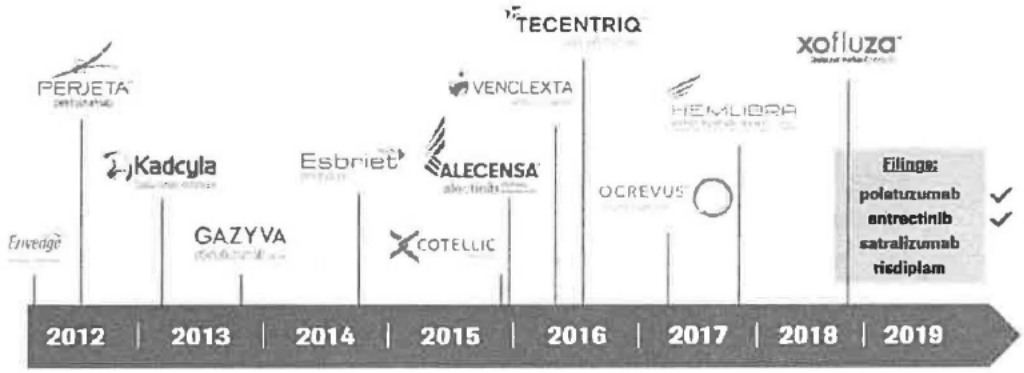
- US: Uptake in non-inhibitors and inhibitors
- EU: Launch in non-inhibitors and Q2W/Q4W dosing

CER=Constant Exchange Rates; Q2w=every 2 weeks dosing; Q4w=every 4 weeks dosing

New products close to annualized sales of CHF 11bn*

Late stage pipeline keeps delivering with 4 NMEs approaching launch





* Venclexta sales are booked by partner AbbVie and therefore not included.

2018: Key late-stage news flow*

	Compound	Indication	Milestone	
Regulatory	**Ocrevus**	RMS / PPMS	EU approval	✓
	Perjeta + Herceptin	Adjuvant HER2+ eBC	EU approval	✓
	Tecentriq + cb/pac +/- Avastin	1L non-sq NSCLC	US/EU filing	✓
	Tecentriq + Avastin	1L RCC	US/EU filing	
	Hemlibra	Hemophilia A inhibitors	EU approval	✓
	Hemlibra	Hemophilia A non-inhibitors	US/EU filing; US approval	✓
	Hemlibra	Every 4 weeks dosing inhibitors/non-inhibitors	US/EU filing	✓
	Xofluza	Acute uncomplicated influenza	US filing	✓
	Venclexta + Rituxan	R/R CLL	US/EU approval	✓
Phase III readouts	**Tecentriq + chemo**	1L non-sq NSCLC	Ph III IMpower130	✓
	Tecentriq + chemo	1L sq NSCLC	Ph III IMpower131	✓
	Tecentriq + chemo	1L non-sq NSCLC	Ph III IMpower132	✓
	Tecentriq + chemo	1L extensive-stage SCLC	Ph III IMpower133	✓
	Tecentriq + nab-pac	1L TNBC	Ph III IMpassion130	✓
	Tecentriq + Cotellic	2/3L CRC	Ph III IMblaze370 / COTEZO	✗
	Actemra	Systemic sclerosis	Ph III focuSSced	✗

Additional 2018 news flow:

- **Actemra**: EU approval of CAR T-cell induced cytokine release syndrome
- **MabThera/Rituxan**: US approval of pemphigus vulgaris
- **Avastin + carboplatin and paclitaxel:** US approval of 1L advanced OC following surgery
- **Gazyva + ibrutinib**: Positive Ph III results in 1L CLL (iLLUMINATE)
- **Venclexta + HMA/LDAC**: Early US filing/approval of PhI/II results in 1L unfit AML
- **polatuzumab vedotin**: Early US filing of Ph II results in R/R DLBCL
- **Hemlibra:** Positive Ph III results in hemophilia A non-inhibitors (HAVEN3/4)
- **entrectinib:** Positive pivotal Ph II results in ROS1+ NSCLC (ALKA, STARTRK1/2)
- **entrectinib:** Positive pivotal Ph II results in NTRK+ tumors (ALKA, STARTRK1/2)
- **risdiplam:** Positive preliminary Ph II/III results in type 1 SMA (FIREFISH)
- **Xofluza:** US approval and positive Ph III results in high risk influeza (CAPSTONE-2)
- **Kadcyla:** Positive Ph III results in eBC (KATHERINE)
- **MabThera/Rituxan:** US approval of rare forms of vasculitis (GPA/MPA)
- **satralizumab:** Positive Ph III results in NMOSD

* Outcome studies are event-driven: timelines may change

2019: Key late-stage news flow*

Roche

	Compound	Indication	Milestone	
Regulatory	**entrectinib**	ROS1+ NSCLC	US filing/approval; EU filing	
	entrectinib	1L NTRK+ pan tumor	US filing/approval; EU filing	
	polatuzumab vedotin	R/R DLBCL	US/EU approval	
	Tecentriq + chemo	1L PDL1+ TNBC	US/EU approval	
	Tecentriq + chemo	1L SCLC	US/EU approval	
	Xofluza	High risk influenza	US approval	
	Kadcyla	Adjuvant HER2+ BC	US filing/approval; EU filing	
	Hemlibra	Non-inhibitors	EU approval	
	Tecentriq + Avastin + chemo	1L NSCLC	EU approval	
	Venclexta + chemo	1L unfit AML	EU filing	
	Venclexta + Gazyva	1L unfit CLL	US/EU filing	
	satralizumab	Neuromyelitis optica spectrum disorders	US/EU filing	
	risdiplam	SMA type 1/2/3	US filing	
Phase III / pivotal readouts	**Tecentriq + Zelboraf +/- Cotellic**	1L BRAF+ Mel, BRAFwt Melanoma	Ph III IMspire150 (TRILOGY) / IMspire170	
	Tecentriq	Adjuvant high-risk MIBC	Ph III IMvigor010	
	Tecentriq + chemo	Neoadjuvant TNBC	Ph III IMpassion031	
	Tecentriq + Avastin	1L HCC	Ph Ib/IMbrave150	
	Venclexta + Gazyva	1L CLL	Ph III CLL14	✔
	Idasanutlin + chemo	R/R AML	Ph III MIRROS	
	Venclexta + chemo	R/R MM	Ph III BELLINI	
	risdiplam	SMA type 2/3	Ph II SUNFISH	

* Outcome studies are event-driven; timelines may change

Roche

Diagnostics Division

Michael Heuer
CEO Roche Diagnostics

2018: Diagnostics Division sales

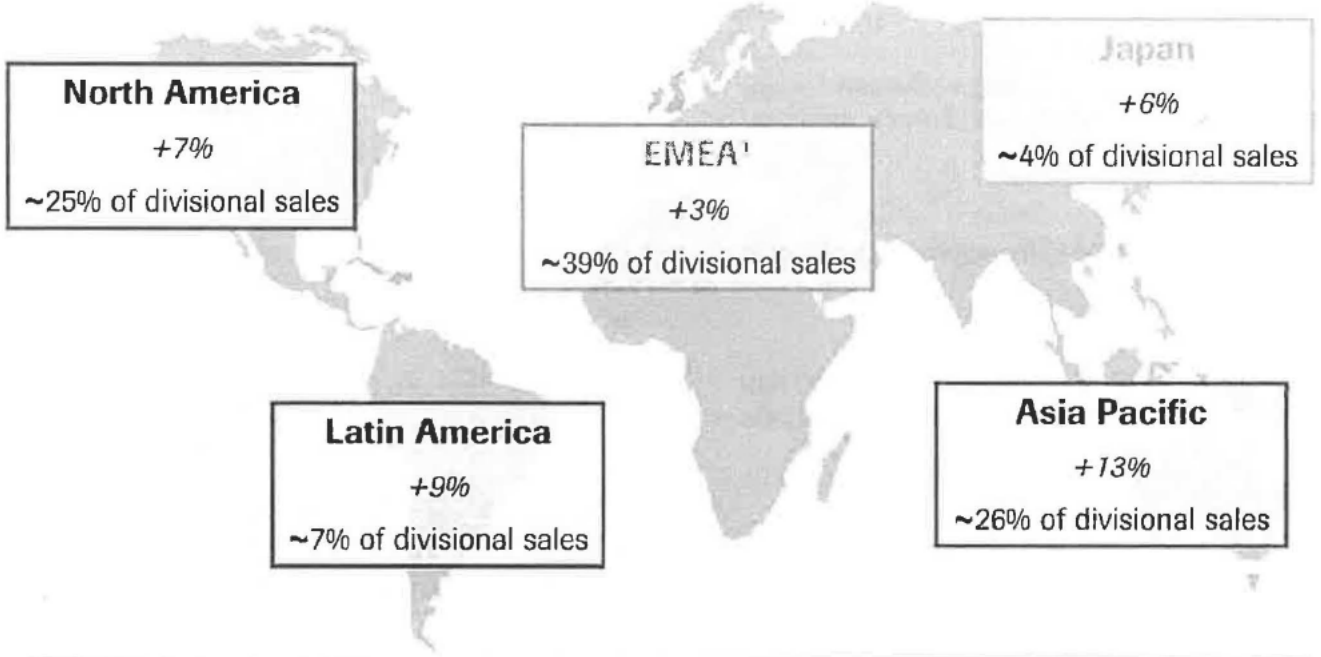
Strong sales growth with all business units contributing

	2018 CHFm	2017 CHFm	Change in % CHF	Change in % CER
Diagnostics Division	**12,879**	**12,079**	**7**	**7**
Centralised and Point of Care Solutions	7,768	7,179	8	8
Molecular Diagnostics	2,019	1,920	5	5
Diabetes Care	1,980	1,965	1	2
Tissue Diagnostics	1,112	1,015	10	10

CER=Constant Exchange Rates; Underlying growth of Molecular Diagnostics excluding sequencing business: +6%

2018: Diagnostics Division regional sales

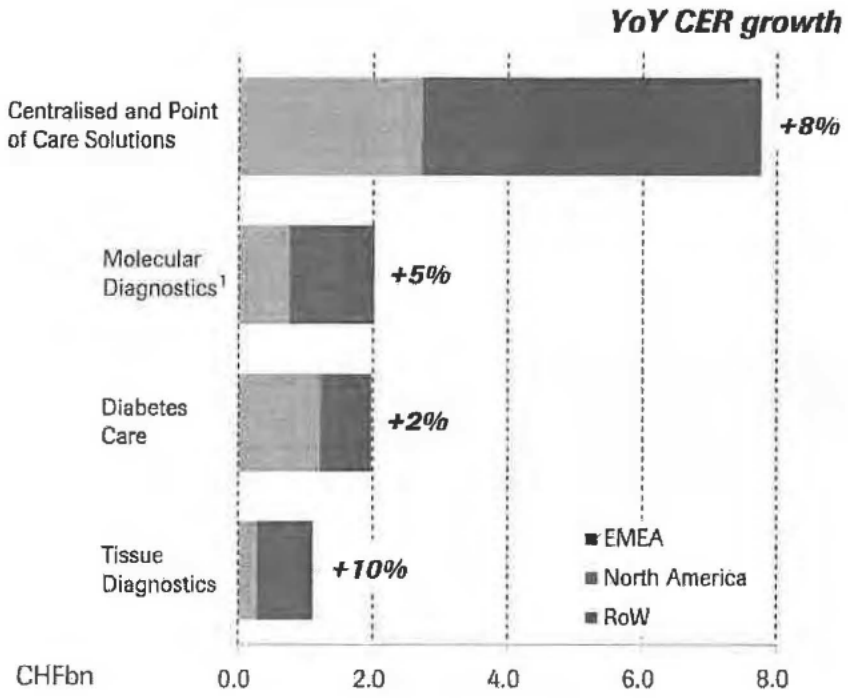
Growth driven by Asia Pacific and North America



¹ Europe, Middle East and Africa; ² Brazil, China, India, Mexico, Russia, South Korea, Turkey; All growth rates at Constant Exchange Rates

2018: Diagnostics Division highlights

Strong growth driven by Centralised and Point of Care Solutions



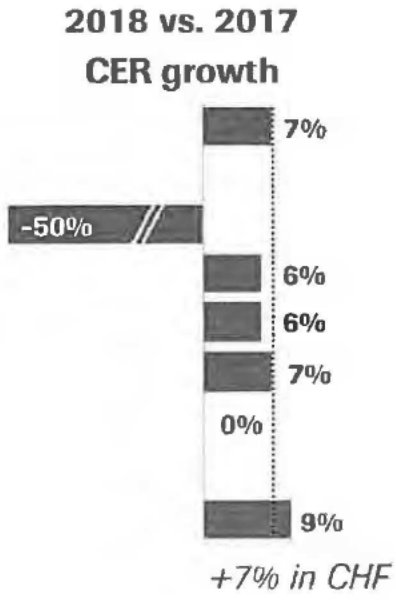
- Immunodiagnostics (+11%); Clinical chemistry (+7%)
- POC MDx[2] (+162%); Blood screening (+9%); Virology (+4%); HPV (+8%)
- Blood glucose monitoring (+2%); insulin delivery systems (-6%)
- Advanced staining (+10%); Companion diagnostics (+9%); Primary staining (+13%)

[1] Underlying growth of Molecular Diagnostics excluding sequencing business: +6%; CER=Constant Exchange Rates; EMEA=Europe, Middle East and Africa; [2] Point of Care Molecular Diagnostics

2018: Diagnostics Division

Core operating profit outgrowing sales

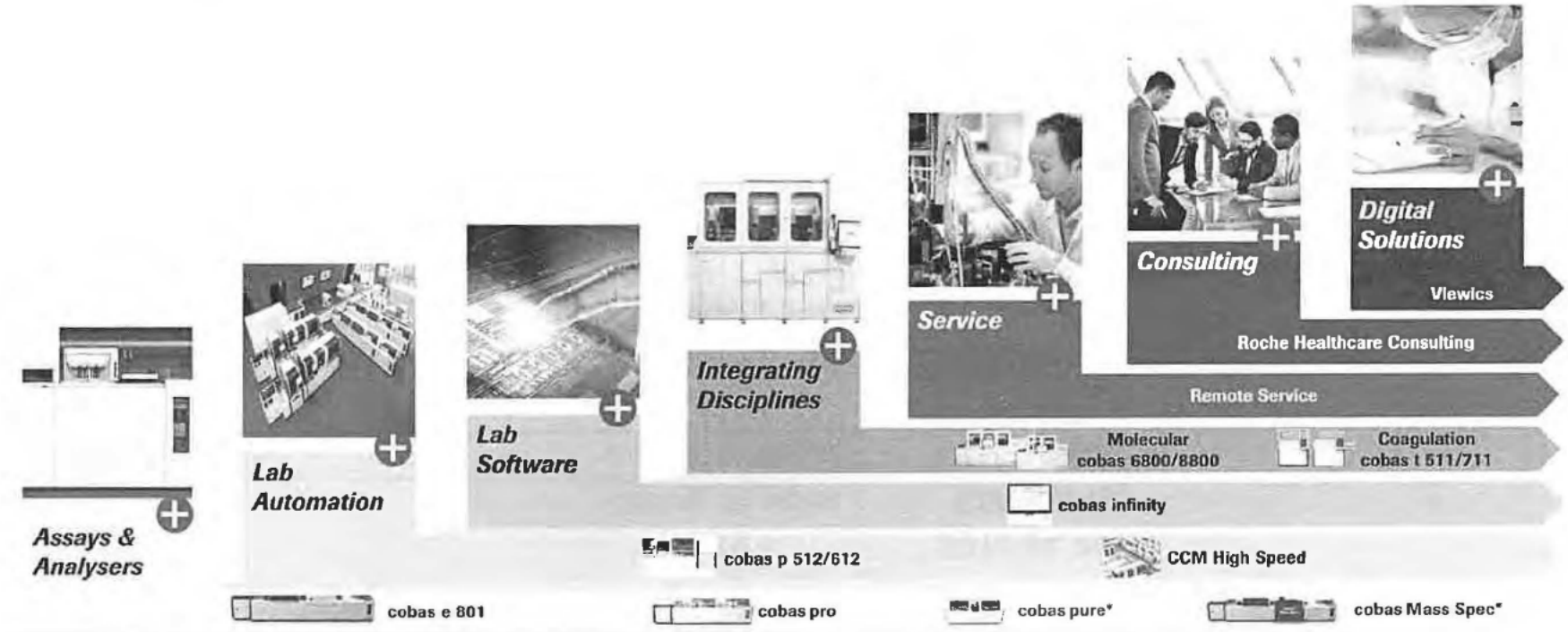
	2018 CHFm	2018 % sales
Sales	**12,879**	**100.0**
Royalties & other op. inc.	82	0.6
Cost of sales	-5,960	-46.3
M & D	-2,966	-23.0
R & D	-1,461	-11.3
G & A	-528	-4.1
Core operating profit	**2,046**	**15.9**



CER=Constant Exchange Rates

Integrated Core Lab

Expansion with additional solutions and entering new disciplines



*cobas pure and cobas Mass Spec have not been launched, yet.

Launch of cobas pro integrated solutions
Next generation medium throughput SWA solution

cobas pro integrated solutions

cobas connection modules (CCM)
cobas p 512, cobas p 612

cobas p 701 post-analytical unit

- Targeting medium to high throughput labs
- New clinical chemistry module cobas c 503 in combination with immunochemistry module cobas e 801
- Substantially higher capacity compared to cobas 6000 on the same footprint
- Enhanced automated procedures such as maintenance, calibration and on-the fly reagent loading

SWA=serum work area

Growth hormone portfolio completed with Elecsys IGFBP-3 test

Providing diagnosis and treatment decisions

Reagent cartridge for Insulin-like growth factor binding protein 3 (IGFBP-3)

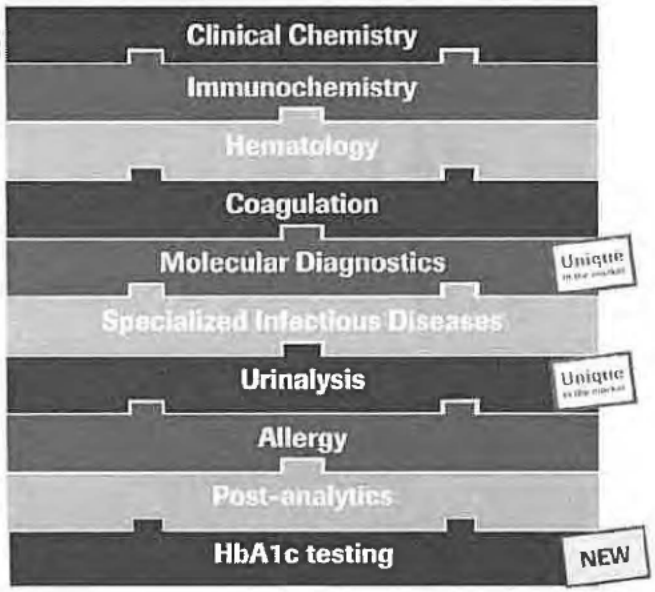
- Complete menu by providing tests for all three main proteins related to growth hormone disorders:
  - Insulin-like growth factor 1 (IGF-1, Somatomedin C)
  - Insulin-like growth factor binding protein 3 (IGFBP-3)
  - Human Growth Hormone (hGH, Somatotropin)
- Available on all cobas e modules

Launch of cobas connection modules (CCM) for cobas c 513

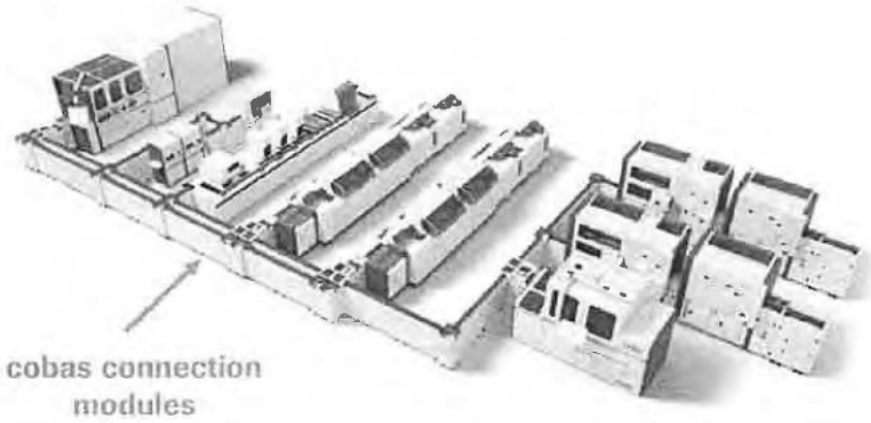
Enabling high throughput diagnosis and monitoring for diabetes

Roche

Multidisciplinary connectivity



Number of CCM installations: >600*

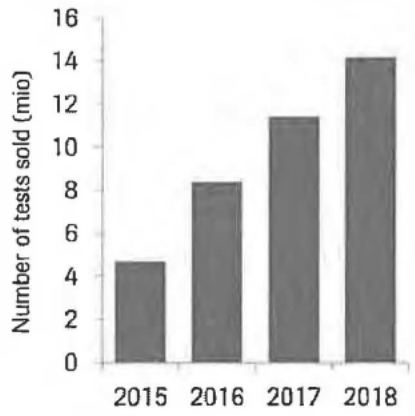


* Life-time installations, June 2018

Global Access Program

Providing access to HIV testing in Africa and beyond

Expanding access



Growing customers

- Tender win for five cobas 8800 and one cobas 6800, Nigeria
- Installation of cobas 8800 at KEMRI/CDC* laboratory, Kenya

Innovation

- Q1 2018 launch of the cobas Plasma Separation Card
- Q4 2018 launch of dried blood spot sample type for early infant diagnosis

*KEMRI: Kenya Medical Research Institute, CDC: Centers for Disease Control

Completing the digital pathology workflow

uPath enterprise software enables automated data analysis and information sharing

- Enhances the efficiency of pathology laboratory workflow with connectivity and automation
- Case management and collaboration between pathologists including remote consultation
- Automated image analysis
- Patient case evaluation and report generation

Key launches 2018

	Area	Product	Market
Instruments/ Devices	Central Laboratory	cobas pro integrated solution – Serum Work Area solution for medium throughput to lower high throughout labs	CE ✓
	Specialty Testing	cobas m 511 – World's first fully digital morphology analyzer and cell counter	US
	Workflow	CCM connectivity to cobas c513 – Connection of cobas c 513 to CCM Automation System for high volume HbA1c testing	WW ✓
	Tissue Dx	BenchMark ULTRA Plus – New and differentiated Advanced Staining System	CE
	Digital Pathology	VENTANA DP200 – Reliable low-volume scanner with superior image quality	CE ✓
	Diabetes Care	Accu-Chek Solo micropump – Small and tubeless insulin delivery device operated through a remote control which includes a blood glucose meter	CE ✓
Tests/ Assays	Endocrinology	IGFBP3 – Completion of the existing growth hormone menu of hGH and IGF-1	CE ✓
	Infectious Diseases	Zika IgG – Highly specific immunoassay for the in vitro qualitative detection of IgG antibodies to Zika virus in human serum and plasma	CE ✓
	Microbiology	cobas CT/NG – Highest throughput CT/NG test on the market with workflow efficiency benefits	US ✓
		cobas 6800/8800 MTB/MAI – High volume solution for MTB/MAI testing; efficient approach to disease management (mixed testing) for infectious disease	CE ✓
	Virology	Plasma Separation Card – Card-like sample collection device; separates plasma from whole blood; for use with CAP/CTM HIV-1 & cobas HIV-1 (6800/8800)	CE ✓
	Sequencing	AVENIO FFPET RUO oncology kits – 3 separate tissue based assay kits for solid tumors	WW ✓
Software	Decision Support	NAVIFY Tumor Board v 1.x – EMR integration	WW ✓

Key launches 2019

	Area	Product	Description	Market[1]
Instruments/ Devices	**Workflow**	cobas prime	Pre-analytical platform to support cobas 6800/8800	CE/US
Tests/ Assays	**Coagulation**	Protein C Chrom	Quantitative determination of protein C in citrated plasma on cobas t 511 / t 711 analyzers	CE
	Microbiology	cobas TV/MG	High volume solution for TV/MG testing; dual-target test with ability to test with CT/NG from the same specimen during the same run	US
		cobas vivoDx MRSA	Live cell assay for prevention and control of MRSA infections	CE
	Tissue Dx	VENTANA HER2 Dual ISH	Fully automated, brightfield ISH assay to determine eligibility for HER2 targeted therapy	CE
Software	**Central Laboratory**	cobas Infinity Central Lab 3.0	One global laboratory middleware solution realizing a very high degree of integration in the laboratory	WW
	Tissue Dx	Algorithm - Breast Panel	Whole slide analysis image analysis algorithm (HER2, ER, PR, Ki-67)	CE
		Algorithm - PD-L1 Lung	Whole slide analysis image analysis algorithm (SP263)	CE
	Sequencing	NAVIFY Mutation Profiler	Software as a medical device for annotating, varient classification, clinical interpretation and reporting from comprehensive genomic profile testing	CE/US
		NAVIFY Therapy Matcher	Informing on treatment options based on local drug labels, medical guidelines and clinical trial outcomes	CE/US
	Decision Support	NAVIFY Tumor Board V2	Integrating a GEHC DICOM imaging viewer into the Tumor Board to support the radiologist	WW
		NAVIFY Oncology Workflow V1	Integration of patient's longitudinal history, diagnosis, and treatment planning by leveraging relevant guidelines	WW
	Diabetes Care	Accu-Chek Sugar View 2.0 (non-ISO)	For non-insulin dependent T2 PwDs, allowing for meter-free blood glucose monitoring using Accu-Chek Active test strips and a smartphone camera	CE

[1] CE: European Conformity, US: FDA approval, WW: Worldwide; GEHC DICOM: GE Healthcare Digital Imaging and Communications in Medicine; T2: Type II Diabetes; PwDs: People with Diabetes

Roche

Finance

Alan Hippe
Chief Financial Officer

2018 results

Focus on Cash

Outlook

2018: Highlights

Roche

Business

- Sales growth of +7%[1] despite biosimilars impact of CHF -1.3bn[1]
- Core operating profit up +9%[1] and Core EPS growth of +19%[1] (+8%[1] excluding US tax reform)
- Dividend in Swiss francs further increased

Cash flow

- Significant cash generation (Operating Free Cash Flow of CHF 18.7bn, +5%[1])
- Net debt lower by CHF 1.3bn vs. YE 2017 as Free Cash Flow of CHF 14.8bn more than offsets dividends paid (CHF -7.3bn) and cash outflow for M&A (CHF -5.7bn)

Net financial results

- Core net financial result improved by +19%[1] due to higher income from equity securities

IFRS

- Net income +24%[1] driven by the operating results and the US tax reform impacts

[1] At Constant Exchange Rates (CER)

2018: Group performance

Strong Core EPS growth (+19%, +8% excl. US tax reform)

	2018 CHFm	2017 CHFm	Change in % CHF	Change in % CER
Sales	**56,846**	**53,299**	**7**	**7**
Core operating profit	**20,505**	**19,012**	**8**	**9**
as % of sales	*36.1*	*35.7*		
Core net income	**15,981**	**13,404**	**19**	**20**
as % of sales	*28.1*	*25.1*		
Core EPS (CHF)	**18.14**	**15.34**	**18**	**19**
IFRS net income	**10,865**	**8,825**	**23**	**24**
Operating free cash flow	**18,741**	**17,827**	**5**	**5**
as % of sales	*33.0*	*33.4*		
Free cash flow	**14,811**	**13,420**	**10**	**11**
as % of sales	*26.1*	*25.2*		

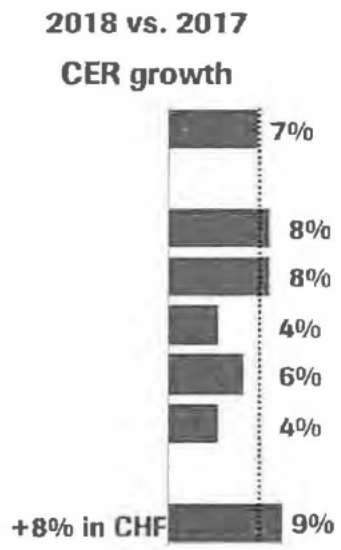
+8% at CER excl. US tax reform

CER=Constant Exchange Rates

2018: Group operating performance

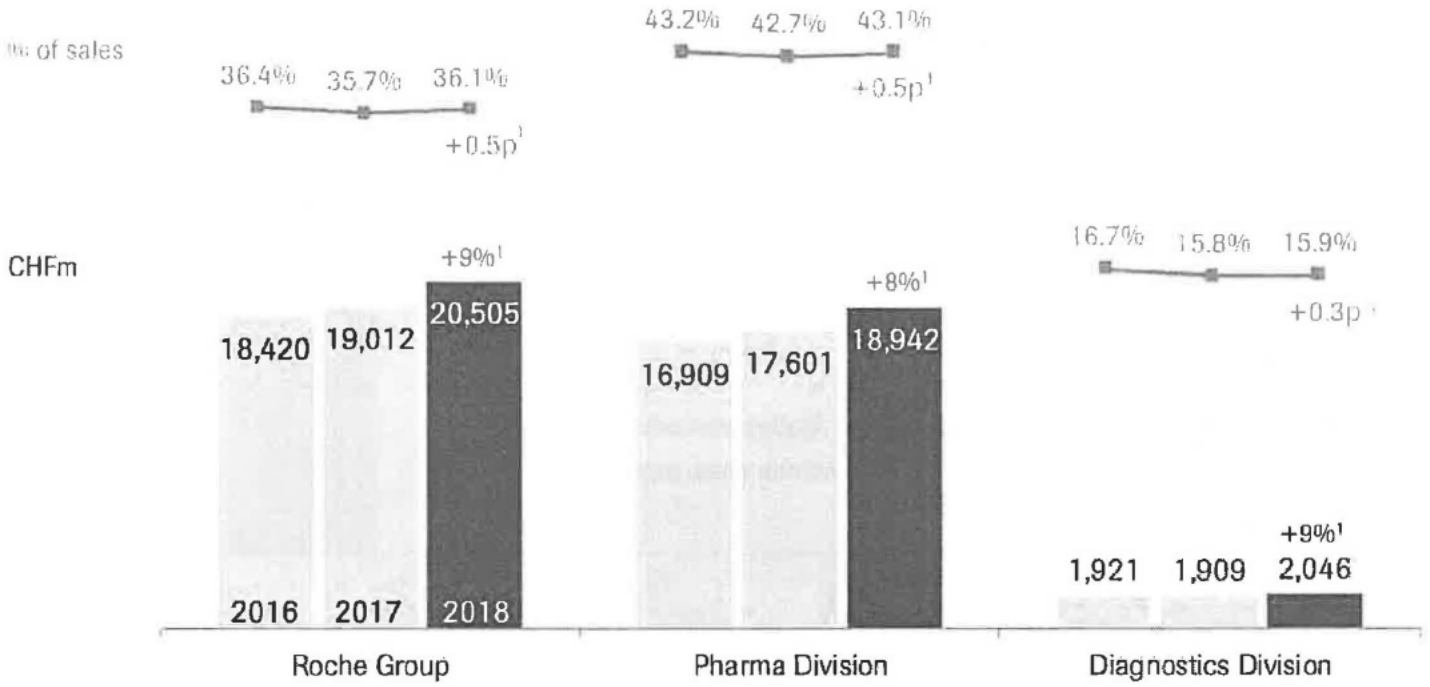
Core operating profit growth ahead of sales growth

	2018 CHFm	2018 abs. CER
Sales	**56,846**	**+3,809**
Royalties & other op. inc.	2,635	+197
Cost of sales	-15,464	-1,185
M & D	-9,905	-418
R & D	-11,047	-641
G & A	-2,560	-93
Core operating profit	**20,505**	**+1,669**
Core OP in % of sales	**36.1**	



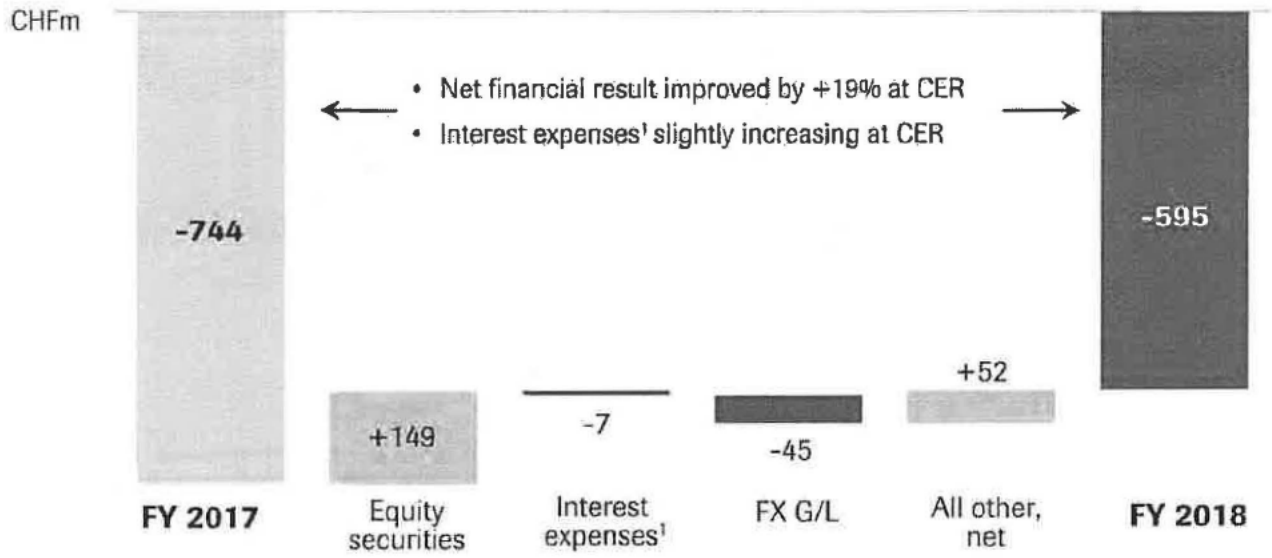
CER=Constant Exchange Rates

2018: Core operating profit and margin further improved



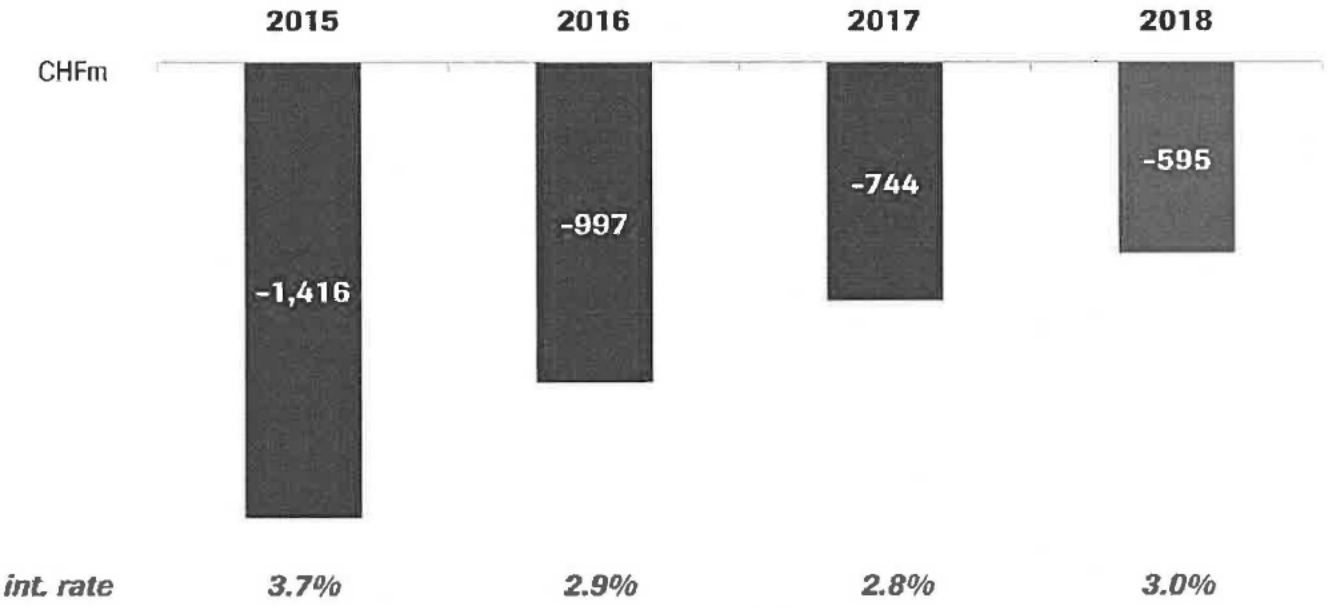
[1] At Constant Exchange Rates (CER)

2018: Core net financial result



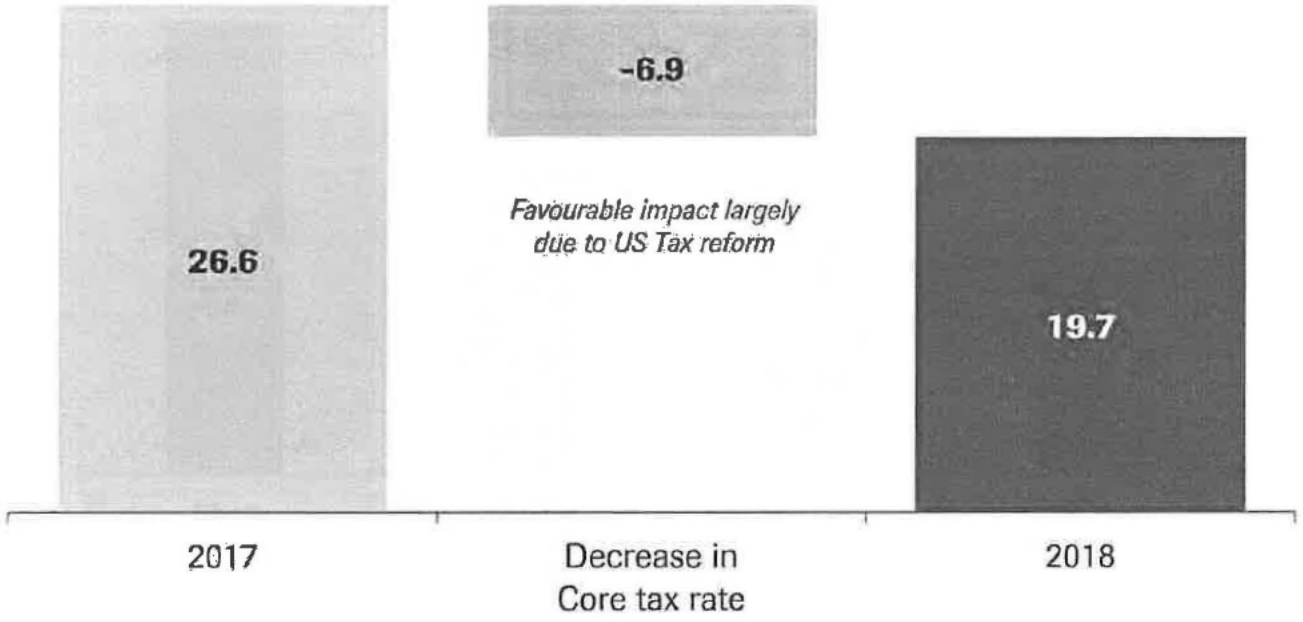
CER = Constant Exchange Rates (avg full year 2017); [1] incl. amortisation of debt discount and net gains on interest rate derivatives

Core net financial result: Continuous improvement



2018: Group Core tax rate

Figures in %



2018: Non-core items; IFRS result impacted by impairments of goodwill & intangible assets

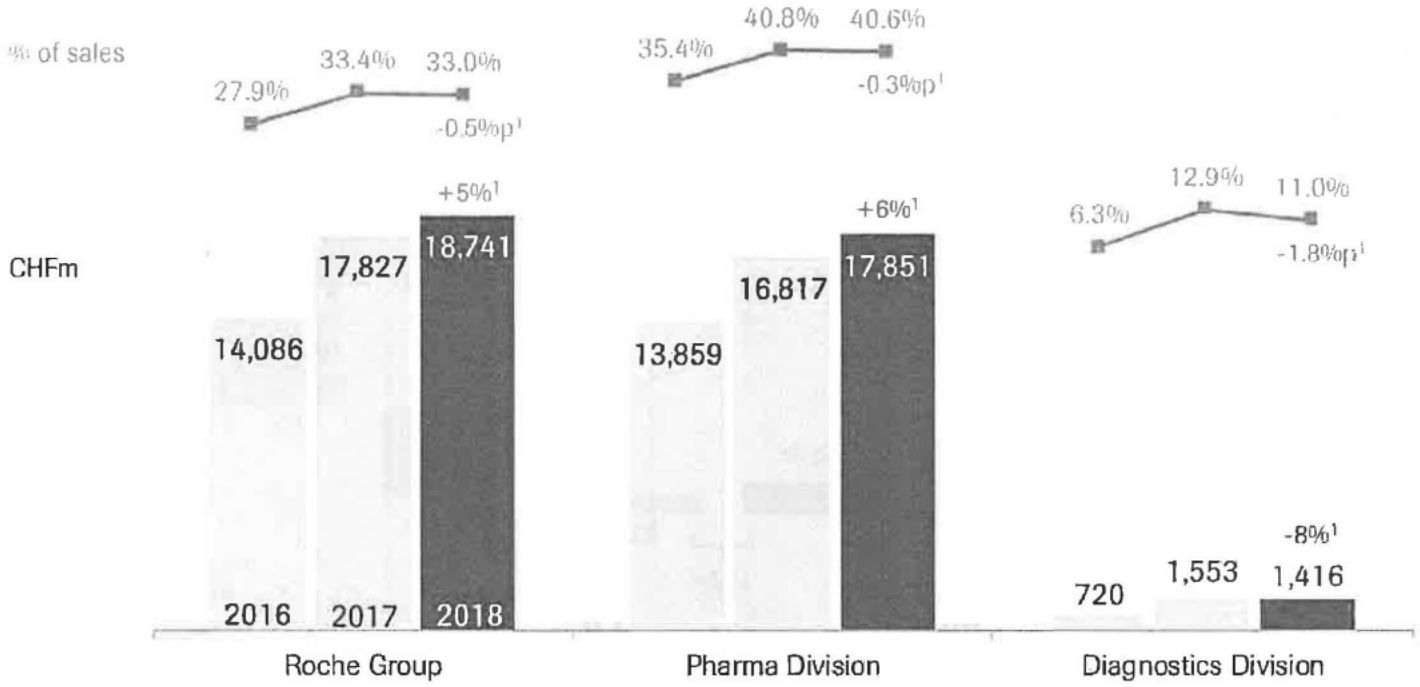
Full Year	2017	2018	CHFm	CHF	CER
Core operating profit	**19,012**	**20,505**	**+1,493**	**+8%**	**+9%**
Global restructuring plans	-1,208	-907	+301		
Amortisation of intangible assets	-1,691	-1,294	+397		
Impairment of intangible assets[1]	-3,518	-3,336	+182		
Alliances & Business Combinations	+350	-35	-385		
Legal & Environmental[2]	+58	-164	-222		
Total non-core operating items	-6,009	-5,736	+273		
IFRS operating profit	**13,003**	**14,769**	**+1,766**	**+14%**	**+15%**
Total financial result & taxes	-4,178	-3,904	+274		
IFRS net income	**8,825**	**10,865**	**+2,040**	**+23%**	**+24%**

CER=Constant Exchange Rates; [1] incl. goodwill [2] incl. pension plan settlements

Focus on Cash

Outlook

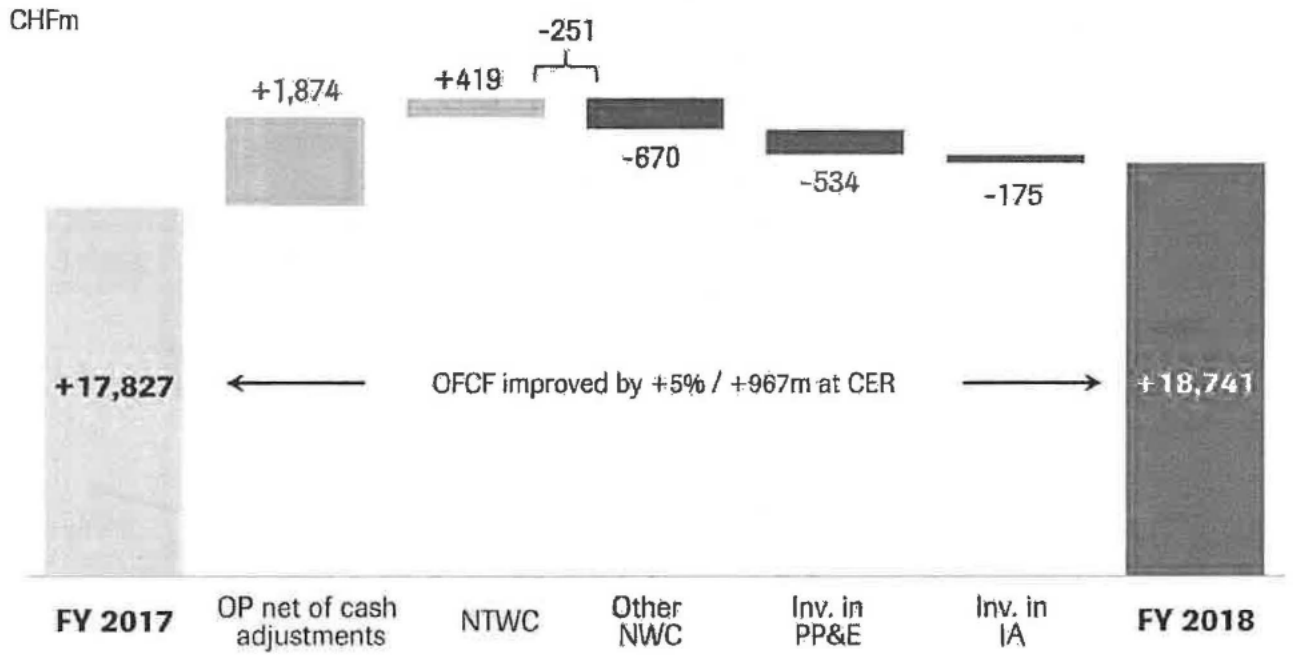
2018: Operating free cash flow and margin



[1] At Constant Exchange Rates (CER)

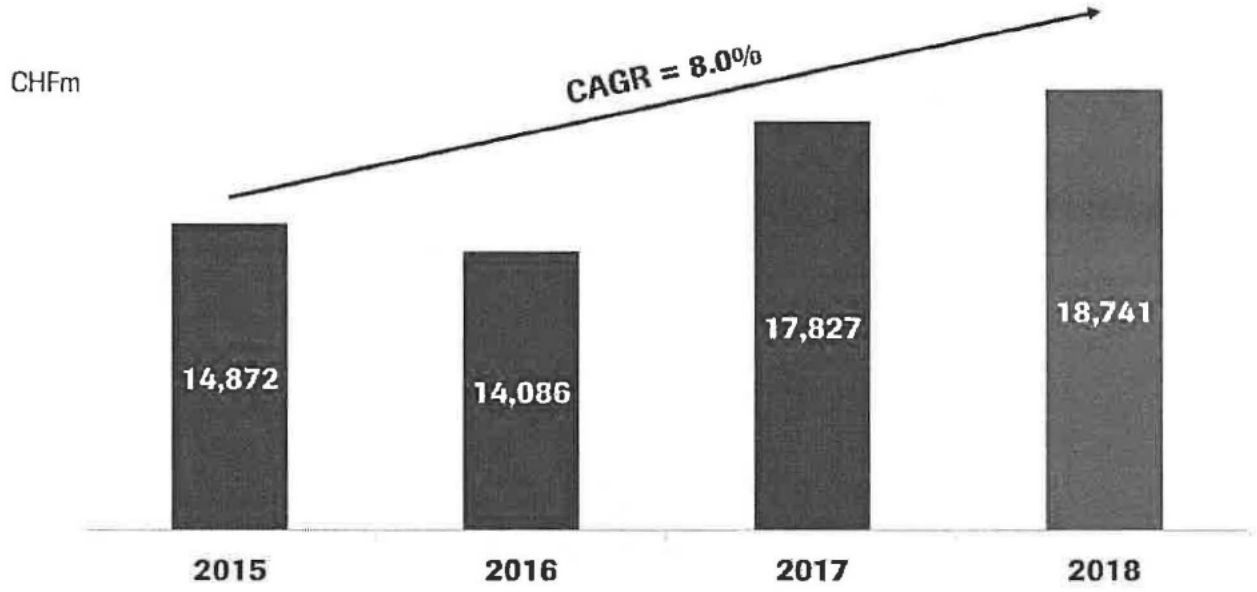
2018: Operating free cash flow

Higher than previous year (+5%) due to higher OP

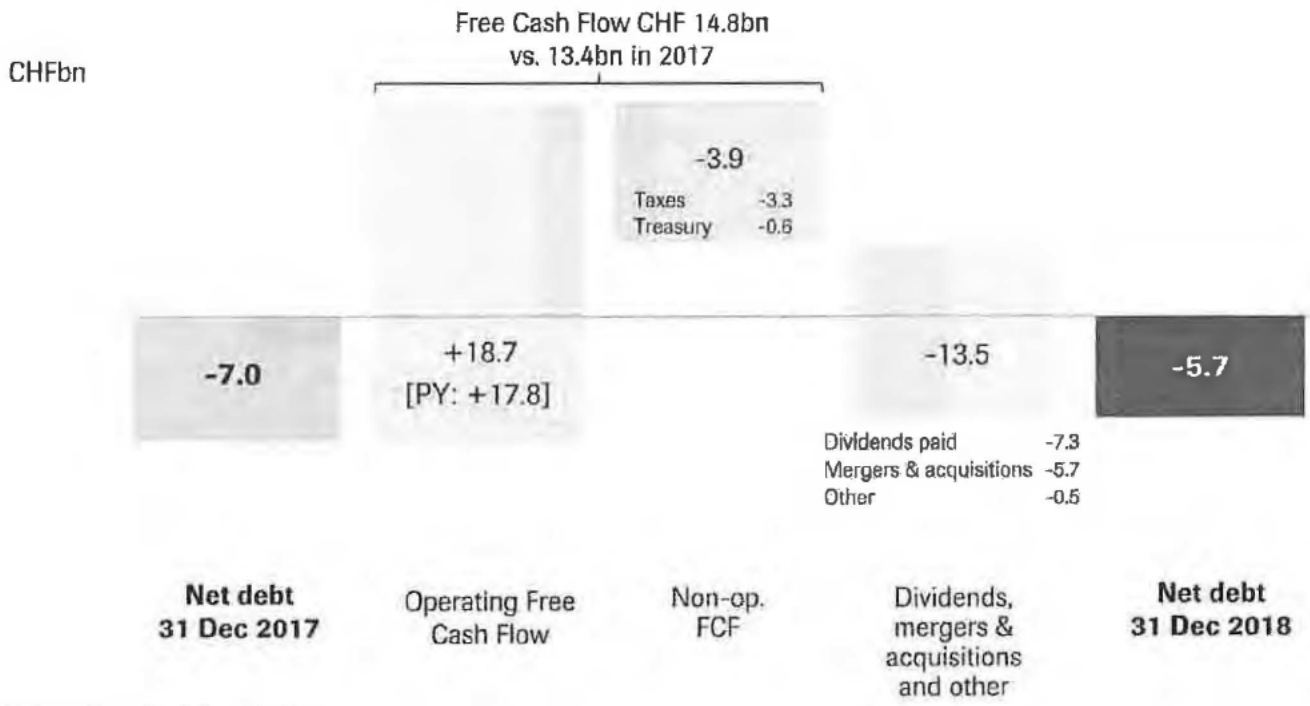


CER = Constant Exchange Rates (avg full year 2017); OP=operating profit; NTWC=net trade working capital; NWC=net working capital; PP&E=property, plant & equipment; IA=intangible assets

Operating free cash flow: Continuous improvement



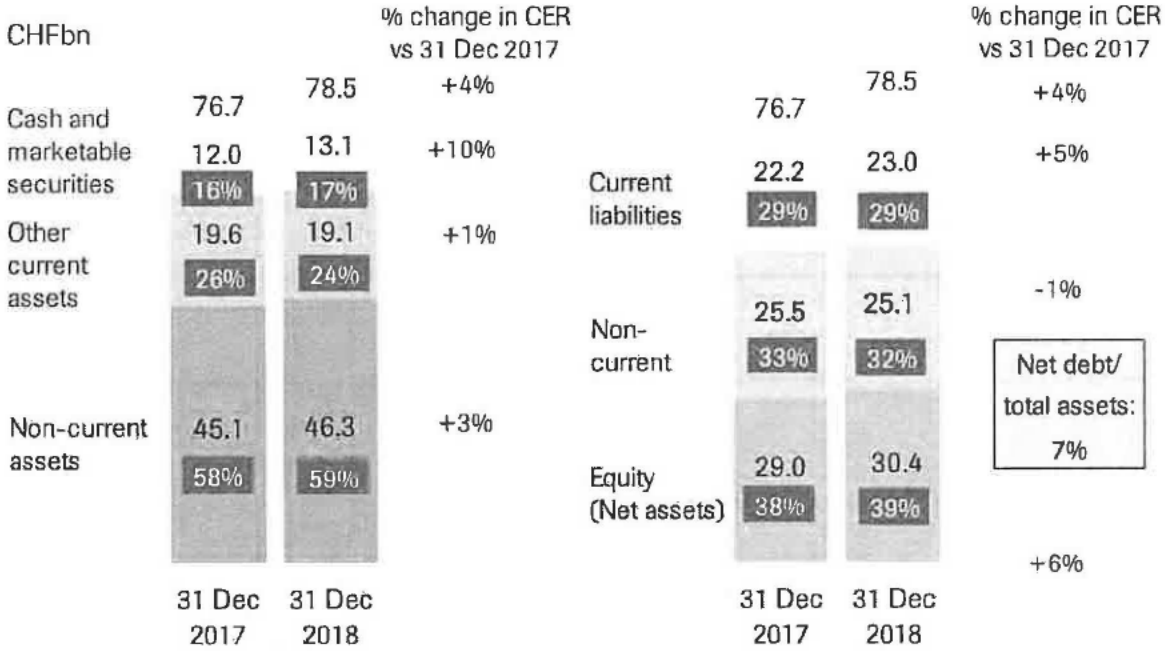
2018: Group net debt lower driven by strong cash generation (CHF 1.3bn vs. YE 2017)



CER = Constant Exchange Rates (avg full year 2017)

Balance sheet 31 December 2018

Equity ratio at 39% (31 December 2017: 38%)



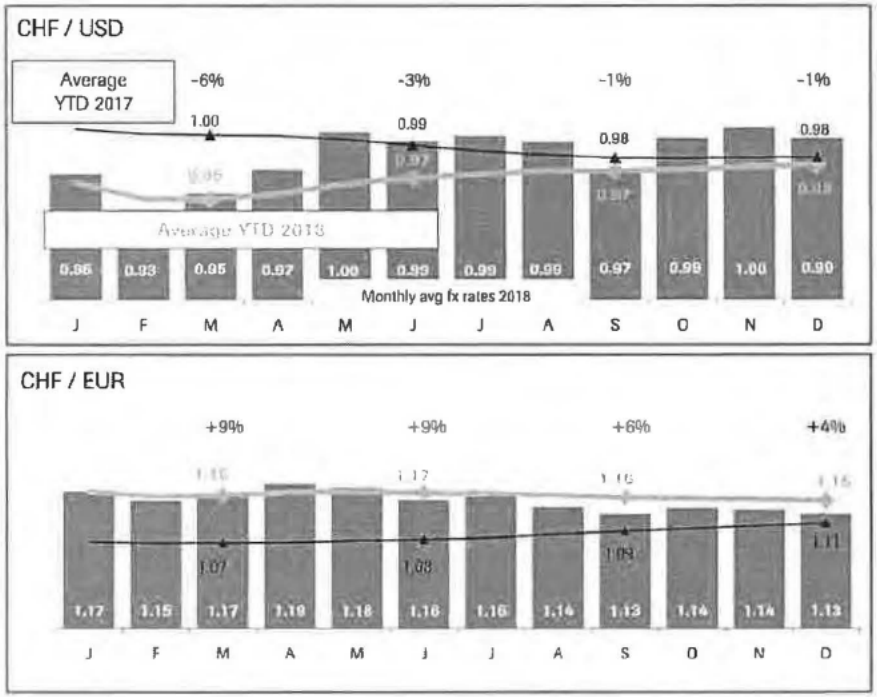
CER = Constant Exchange Rates (avg full year 2017)

2018 results

Focus on Cash

Outlook

Low currency impact in 2018



In 2018 impact is (%p):

	Q1	HY	Sep YTD	FY
Sales	**-1**	**0**	**0**	**0**
Core operating profit		**0**		**-1**
Core EPS		**1**		**-1**

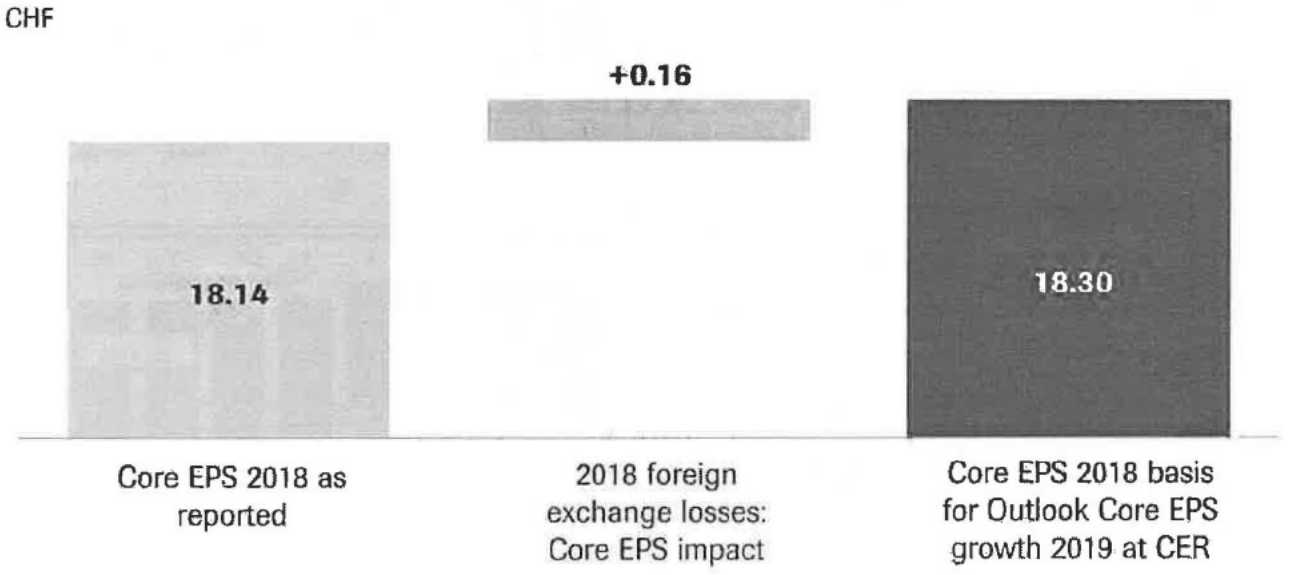
***2019** currency impact[1] expected (based on **31 Dec 2018** FX rates):*

- Around -1%p FX impact on Sales, Core OP & Core EPS

[1] On group growth rates

2018: Core EPS

Core EPS 2018 of CHF 18.30 is basis for Core EPS outlook 2019 at CER



CER=Constant Exchange Rates (avg full year 2018)

2019 outlook

Group sales growth[1]	• Low-to mid-single digit
Core EPS growth[1]	• Broadly in line with sales
Dividend outlook	• Further increase dividend in Swiss francs

[1] At Constant Exchange Rates (CER)

Roche

Pipeline summary

Changes to the development pipeline
FY 2018 update

Roche

New to phase I

3 NMEs:
RG6217 - HBV
RG6237 - neuromuscular disorders
RG7769 PD1-TIM3 biMAb - solid tumors
1 AI:
RG7601 Venclexta + gilteritinib – r/r AML

New to phase II

2 NMEs transitioned from Ph1
RG7906 - psychiatric disorders
RG6058 tiragolumab + Tecentriq - NSCLC
1 NME starting Ph2
RG6180 iNeST (personalized cancer vaccine) + pembrolizumab - malignant melanoma
1 NME following termination of Ph3
RG7412 crenezumab – familial Alzheimer's disease healthy individuals

1 AI:
RG7446 Tecentriq SC – NSCLC

New to phase III

1 NME transitioned from Ph2:
RG6042 HTT ASO - Huntington's
6 AIs:
RG7446 Tecentriq – Her2-pos. BC neoadj
RG7446 Tecentriq – high risk NMIBC
RG6152 Xofluza - influenza hosp. patients
RG6152 Xofluza – influenza pediatric patients
RG7601 Venclexta - r/r MM t(11:14)
RG7601 Venclexta + HMA/LDAC - 1L AML*

New to registration

2 NMEs + 1 AI transitioned from Ph2 following filing in EU and US:
RG7596 polatuzumab vedotin - r/r DLBCL
RG6268 entrectinib - NSCLC ROS1+
RG6268 entrectinib – NTRK1 pan-tumor
3 AIs transitioned from Ph3 following filing in EU and US:
RG7446 Tecentriq + nab-paclitaxel 1L non sq NSCLC
RG7446 Tecentriq + nab-paclitaxel 1LTNBC
RG7446 Tecentriq + chemo - 1L extensive stage SCLC

Removed from phase I

2 NMEs:
RG7813 CEA IL2vFP + Tecentriq – solid tumors
RG6080 nacubactam – bacterial infections
2 AIs:
RG7876 selicrelumab + Tecentriq - solid tumors
RG7446 T+ Gazyva / tazemetostat – r/r DLBCL & FL

Removed from phase II

1 NME:
PRO VAP 1 inhibitor - inflammatory diseases
1AI:
RG7601 Venclexta + Rituxan +/- bendamustine - r/r FL

Removed from phase III

1 NME:
RG7412 crenezumab – Alzheimer's disease

Removed from registration

2 AIs following US approval:
RG1569 Actemra autoinjector - RA
RG7601 Venclexta + HMA/LDAC -1L AML
1 AIs following EU approval:
RG7601 Venclexta + Rituxan - r/r CLL

Status as of January 31, 2019

*study ongoing and lead by Abbvie

Roche Group development pipeline

Phase I (40 NMEs + 21 AIs)

RG6026	CD20 TCB ± chemo ± T	heme tumors
RG6109	-	AML
RG6114	mPI3K alpha inh	HR+ BC
RG6123	-	solid tumors
RG6146	BET inh combos	solid & heme tumors
RG6148	-	HER2 expressing BC
RG6160	-	multiple myeloma
RG6171	SERD (3)	ER+ (HER2-) mBC
RG6180	iNeST*± T	solid tumors
RG6185	pan-RAF inh + Cotellic	solid tumors
RG6194	HER2/CD3 TDB	BC
RG7159	anti-CD20 combos	heme tumors
RG7421	Cotellic + Zelboraf + T	melanoma
	Cotellic + T	2L BRAF WT mM
	Cotellic + T	RCC, bladder, head & neck ca
RG7440	ipatasertib + Taxane + T	TNBC
RG7446	Tecentriq (T)	solid tumors
	Tecentriq (T)	NMIBC
	T-based Morpheus platform	solid tumors
	T + Avastin + Cotellic	2/3L CRC
	T ± Avastin ± chemo	HCC, GC, PaC
	T + Tarceva/Alecensa	NSCLC
	T + anti-CD20 combos	heme tumors
	T ± lenalidomide ± daratumumab	MM
	T + K/HP	HER2+ BC
	T + radium 223	mCRPC
	T + rucaparib	ovarian ca
RG7461	FAP IL2v FP combos	solid tumors
RG7601	Venclexta + idasanutlin	AML
	Venclexta ± azacitidine	r/r MDS
	Venclexta + gilteritinib	r/r AML
	Venclexta + Cotellic + T	MM
RG7769	PD1-TIM3 biMAb	solid tumors
RG7802	cibisatamab ± T	solid tumors
RG7827	FAP-4-1BBL FP	solid tumors
RG7828	mosunetuzumab ± T	heme tumors
RG7876	selicrelumab + Avastin	solid tumors
CHU	Raf/MEK dual inh	solid tumors
CHU	glypican-3/CD3 biMAb	solid tumors
CHU	codrituzumab	HCC
RG6107	C5 inh MAb	PNH
RG6151	-	asthma
RG6173	-	asthma
RG6174	-	inflammatory diseases
RG7835	-	autoimmune diseases
RG7880	IL-22Fc	inflammatory diseases
RG6004	HBV LNA	HBV
RG6217	-	HBV
RG7854	TLR7 agonist (3)	HBV
RG7861	anti-*S. aureus* TAC	infectious diseases
RG7907	HBV CpAM (2) (Capsid)	HBV
RG7992	FGFR1/KLB MAb	metabolic diseases
RG6000	-	ALS
RG6049	-	neurodegenerative disorder
RG6237	-	neuromuscular disorder
RG7816	GABA Aa5 PAM	autism
RG6147	-	geographic atrophy
RG7774	-	retinal disease
CHU	PTH1 recep. ago	hypoparathyroidism
CHU	-	hyperphosphatemia
CHU	-	endometriosis

Phase II (13 NMEs + 10 AIs)

RG6180	iNeST* + pembrolizumab	malignant melanoma
RG6058	tiragolumab ± T	NSCLC
RG7388	idasanutlin	polycythemia vera
RG7421	Cotellic + Tecentriq ± taxane	TNBC
RG7440	ipatasertib	TNBC neoadj
RG7446	Tecentriq SC	NSCLC
RG7596	polatuzumab vedotin	r/r FL
RG7601	Venclexta + Rituxan	DLBCL
	Venclexta + azacitidine	1L MDS
	Venclexta + fulvestrant	2L HR+BC
RG6149	ST2 MAb	asthma
RG7159	obinutuzumab	lupus
RG7625	petosicatib	autoimmune diseases
RG7845	fenebrutinib	RA, lupus, CSU
CHU	nemolizumab[#]	pruritus in dialysis patients
NOV	TLR4 MAb	autoimmune diseases
RG1662	basmisanil	CIAS
RG6100	Tau MAb	Alzheimer's
RG7412	crenezumab	familial Alzheimer's healthy pts
RG7916	risdiplam[§]	SMA
RG7906	-	psychiatric disorders
RG7935	prasinezumab	Parkinson's
RG7716	faricimab	wAMD

New Molecular Entity (NME)
Additional Indication (AI)
Oncology
Immunology
Infectious Diseases
CardioMetabolism
Neuroscience
Ophthalmology
Other

RG-No - Roche/Genentech NOV- Novimmune managed [§]Ph2 pivotal [#]Individualized NeoAntigen Specific Immunotherapy, formerly PCV

CHU- Chugai managed *out-licensed to Goldderma and Maruho AD TDB=T-cell dependent bispecific T=Tecentriq; TCB=T-cell bispecific

Status as of January 31, 2019

Roche Group development pipeline

Roche

Phase III (11 NMEs + 35 AIs)

RG3502	Kadcyla	HER2+ eBC
	Kadcyla + Perjeta	HER2+ eBC
RG6284	Perjeta + Herceptin FDC SC	HER2+ BC
RG7388	idasanutlin + chemo	AML
RG7440	ipatasertib + abiraterone	1L CRPC
	ipatasertib + chemo	1L TNBC/HR+ BC
RG7421	Cotellic + Zelboraf+T	1L BRAFm melanoma
	Cotellic + T	1L BRAF WT melanoma
RG7596	polatuzumab vedotin	1L DLBCL
RG7446	Tecentriq	NSCLC adj
	Tecentriq	MIBC adj
	Tecentriq	NMIBC, high risk
	Tecentriq Dx+	1L sq + non-sq NSCLC
	Tecentriq	RCC adj
	T + chemo + Avastin	1L ovarian cancer
	T + pemetrexed	1L non-sq NSCLC
	T + nab-paclitaxel	1L sq NSCLC
	T ± chemo	SCCHN adj
	Tecentriq	HER2+ BC neoadj
	T + paclitaxel	1L TNBC
	T + capecitabine or carbo/gem	1L TNBC
	T + paclitaxel	TNBC adj
	T + nab-paclitaxel	TNBC neoadj
	T + Avastin	1L HCC
	T + Avastin	RCC
	T ± chemo	1L mUC
	T + enzalutamide	CRPC
RG7446/RG7853/ RG6268	Tecentriq or Alecensa or entrectinib	1L NSCLC Dx+
RG7601	Venclexta + Gazyva	1L CLL
	Venclexta + bortezomib	MM
	Venclexta	r/r MM t(11;14)
	Venclexta + HMA/LDA	1L AML
RG7853	Alecensa	NSCLC adj
RG3648	Xolair	nasal polyps
RG7413	etrolizumab	ulcerative colitis
	etrolizumab	Crohn's
RG6152	Xofluza	influenza, high risk
	Xofluza	influenza, hospitalized pts
	Xofluza	influenza, pediatric
RG1450	gantenerumab	Alzheimer's
RG6042	HTT ASO	Huntington's
RG6168	satralizumab	NMOSD
RG6206	anti-myostatin adnectin	DMD
RG7314	balovaptan	autism
RG3645	port delivery system with ranibizumab	wAMD
RG7716	faricimab	DME

Registration (3 NMEs + 8 AIs)

RG6013	Hemlibra[1]	hemophilia A w/o FVIII inh
	Hemlibra[1]	Q4W hemophilia A
RG6268	entrectinib	NSCLC ROS1+
	entrectinib	NTRK1 pantumor
RG7446	T + chemo + Avastin[1]	1L non-sq NSCLC
	T + nab-paclitaxel	1L non-sq NSCLC
	T + nab-paclitaxel	1L TNBC
	T + chemo	1L extensive stage SCLC
RG7596	polatuzumab vedotin	r/r DLBCL
RG105	MabThera[1]	pemphigus vulgaris
RG6152	Xofluza [1]	influenza

[1] Approved in US

New Molecular Entity (NME)
Additional Indication (AI)
Oncology
Immunology
Infectious Diseases

CardioMetabolism
Neuroscience
Ophthalmology
Other

RG-No Roche/Genentech
CHU Chugai managed
NOV Novimmune managed

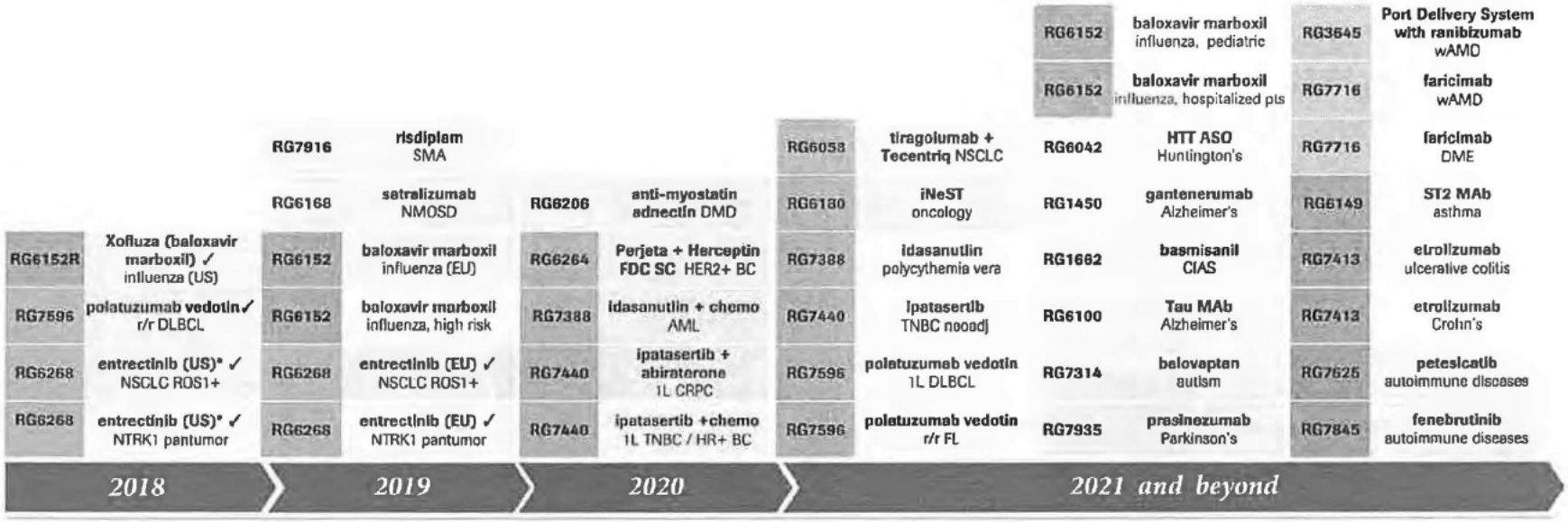
[4]out-licensed to Galderma and Maruho AD
FDC=fixed-dose combination

T=Tecentriq; TCB=T-cell bispecific
TDB=T-cell dependent bispecific

Status as of January 31, 2019

NME submissions and their additional indications

Projects currently in phase II and III



*pending FDA acceptance of filing

✓ Indicates submission to health authorities has occurred
Unless stated otherwise submissions are planned to occur in US and EU

New Molecular Entity (NME)
Additional Indication (AI)
Oncology
Immunology
Infectious Diseases
CardioMetabolism
Neuroscience
Ophthalmology
Other
FDC = fixed-dose combination

Status as of January 31, 2019

AI submissions for existing products

Projects currently in phase II and III

Roche

2018

- RG105 — MabThera (EU) ✓ pemphigus vulgaris
- RG1569 — Actemra auto injector (US) RA ✓
- RG1569 — Actemra (EU) ✓ CRS
- RG3648 — Xolair PFS (US) ✓ Asthma & CIU
- RG6013 — Hemlibra ✓ hemophilia A FVIII non-inh
- RG6013 — Hemlibra ✓ hemophilia A, Q4W
- RG7601 — Venclexta + Rituxan (EU) ✓ r/r CLL
- RG7601 — Venclexta + HMA/LDAC (US) ✓ 1L AML
- RG7446 — Tecentriq + chemo + Avastin ✓ 1L non-sq NSCLC
- RG7446 — Tecentriq + nab-paclitaxel 1L non-sq NSCLC ✓
- RG7446 — Tecentriq + chemo ✓ 1L extens. stage SCLC
- RG7446 — Tecentriq + nab-paclitaxel 1L TNBC ✓

2019

- RG3648 — Xolair nasal polyps
- RG3502 — Kadcyla HER2+ eBC
- RG7446 — Tecentriq + Avastin 1L HCC
- RG7421 — Cotellic + Tecentriq 1L BRAF WT melanoma
- RG7421 — Cotellic + Tecentriq + Zelboraf 1L BRAFmut melanoma
- RG7446 — Tecentriq 1L non-sq + sq NSCLC (Dx+)
- RG7446 — Tecentriq + nab-paclitaxel TNBC neoadj
- RG7446 — Tecentriq + nab-paclitaxel 1L sq NSCLC
- RG7446 — Tecentriq + pemetrexed 1L non-sq NSCLC
- RG7601 — Venclexta + Gazyva 1L CLL
- RG7601 — Venclexta + bortezomib MM

2020

- RG3502 — Kadcyla + Perjeta HER2+ eBC
- RG7446 — Tecentriq + Avastin RCC
- RG7446 — Tecentriq + paclitaxel 1L TNBC
- RG7446 — Tecentriq MIBC adj
- RG7446 — Tecentriq ± chemo 1L mUC
- RG7446 — Tecentriq + enzalutamide CRPC
- RG7446 — Tecentriq + chemo + Avastin 1L ovarian cancer

2021 and beyond

- RG7446/ RG7853/ RG6268 — Tecentriq or Alecensa or entrectinib 1L NSCLC Dx+
- RG7446 — Tecentriq SC NSCLC
- RG7446 — Tecentriq NSCLC adj
- RG7446 — Tecentriq HER2+ BC neoadj
- RG7446 — Tecentriq + paclitaxel TNBC adj
- RG7446 — Tecentriq High risk NMIBC
- RG7446 — Tecentriq RCC adj
- RG7446 — Tecentriq + chemo SCCHN adj
- RG7446 — Tecentriq + capecitabine or carbo/gem TNBC
- RG7159 — obinutuzumab lupus nephritis
- RG7421 — Cotellic + Tecentriq ± taxane TNBC
- RG7601 — Venclexta + HMA/LDAC 1L AML
- RG7601 — Venclexta r/r MM t(11:14)
- RG7601 — Venclexta + Rituxan DLBCL
- RG7601 — Venclexta + azacitidine 1L MDS
- RG7601 — Venclexta+ fulvestrant 2L HR+BC
- RG7853 — Alecensa NSCLC adj

✓ Indicates submission to health authorities has occurred
Unless stated otherwise submissions are planned to occur in US and EU

New Molecular Entity (NME)
Additional Indication (AI)
Oncology
Immunology
Infectious Diseases
CardioMetabolism
Neuroscience
Ophthalmology
Other

Status as of January 31, 2019

Cancer immunotherapy pipeline overview

Phase I (10 NMEs + 26 AIs)

RG6026	CD20 TCB± chemo ± T	heme tumors
RG6123	–	solid tumors
RG6160	–	multiple myeloma
RG6180	INeST (PCV) ± T	solid tumors
RG6194	HER2/CD3 TDB	BC
RG7421	Cotellic + Zelboraf + T	melanoma
	Cotellic + T	2L BRAF WT mM
	Cotellic + T	RCC, bladder, head & neck ca
RG7440	ipatasertib + Taxane + T	TNBC
RG7446	Tecentriq (T)	solid tumors
	Tecentriq (T)	NMIBC
	T-based Morpheus platform	solid tumors
	T + Avastin + Cotellic	2/3L CRC
	T ± Avastin ± chemo	HCC, GC, PaC
	T + Tarceva/Alecensa	NSCLC
	T + anti-CD20 combos	heme tumors
	T ± lenalidomide ± daratumumab	MM
	T + K/HP	HER2+ BC
	T + radium 223	mCRPC
	T + rucaparib	ovarian ca
RG7461	FAP IL2v FP combos	solid tumors
RG7601	Venclexta + Cotellic/idasanutlin	AML
	Venclexta + Cotellic + T	MM
RG7769	PD1-TIM3 biMAb	solid tumors
RG7802	cibisatamab ± T	solid tumors
RG7827	FAP-4-1BBL FP	solid tumors
RG7828	mosunetuzumab ± T	heme tumors
RG7876	selicrelumab + Avastin	solid tumors

AMGN**	Tecentriq + talimogene laherp	TNBC, CRC
BLRX**	Tecentriq + BL-8040	AML, solid tumors
CRVS**	Tecentriq + CPI-444	solid tumors
EXEL**	Tecentriq + cabozantinib	solid tumors
HALO**	Tecentriq + PEGPH20	CCC, GBC
INO**	Tecentriq + INO5401+INO9012	bladder ca
KITE**	Tecentriq + KTE-C19	r/r DLBCL

MORPHEUS Platform - Phase Ib/II (6 AIs)

RG7446	T-based Morpheus	pancreatic cancer
	T-based Morpheus	gastric cancer
	T-based Morpheus	HR+ BC
	T-based Morpheus	NSCLC
	T-based Morpheus	2L TNBC
	T-based Morpheus	CRC

Phase II (2 NMEs + 6 AIs)

RG6180	INeST (PCV)+ pembrolizumab	malignant melanoma
RG6058	tiragolumab ± T	NSCLC
RG7421	Cotellic + Tecentriq ± taxane	TNBC
RG7446	Tecentriq SC	NSCLC
Gradalis**	Tecentriq + Vigil	ovarian ca
GTHX**	Tecentriq + trilaciclib	SCLC
IMDZ**	Tecentriq + NY-ESO-1	soft tissue sarcoma
SNDX**	Tecentriq + entinostat	TNBC

** External collaborations: AMGN – Amgen oncolytic virus; BLRX - BioLine Rx CXCR4 antag; CRVS - Corvus ADORA2A antag; EXEL - Exelexis' TKI; Gradalis – EATC therapy; GTHX - G1 Therapeutics CDK4/6; HALO - Halozyme PEGPH20; IMDZ - Immune Design CMB305; INO - Inovio T cell activating immunotherapy (INO-5401), IL-12 activator (INO-9012); JNJ - Janssen CD38 MAb; KITE – Kite KTE-C19; SNDX – Syndax HDAC inh

New Molecular Entity (NME)
Additional Indication (AI)
Oncology

RG-No Roche/Genentech

T=Tecentriq; TCB=T-cell bispecific
TDB=T-cell dependent bispecific

Phase III (21 AIs)

RG7421	Cotellic+Zelboraf+T	1L BRAFm melanoma
	Cotellic + T	1L BRAF WT melanoma
RG7446	Tecentriq	NSCLC adj
	Tecentriq	MIBC adj
	Tecentriq	high risk NMIBC
	Tecentriq Dx+	1L sq + non-sq SCLC
	Tecentriq	RCC adj
	T + chemo+ Avastin	1L ovarian cancer
	T + pemetrexed	1L non-sq NSCLC
	T + nab-paclitaxel	1L sq NSCLC
	T ± chemo	SCCHN adj
	Tecentriq	HER2-pos. BC neoadj
	T + nab-paclitaxel	1L TNBC
	T + capecitabine or carbo/gem	1L TNBC
	T + paclitaxel	TNBC adj
	T + nab-paclitaxel	TNBC neoadj
	T + Avastin	RCC
	T + Avastin	1L HCC
	T ± chemo	1L mUC
	T + enzalutamide	CRPC
RG7446/RG7853/ RG6268	Tecentriq or Alecensa or entrectinib	1L NSCLC Dx+

Registration (4 AIs)

RG7446	T + chemo + Avastin	1L non-sq NSCLC
	T + nab-paclitaxel	1L non-sq NSCLC
	T + chemo	1L extensive stage SCLC
	T + nab-paclitaxel	1L TNBC

Status as of January 31, 2019

Major granted approvals 2018

Approved

US		EU		Japan-Chugai	
RG3645	**Lucentis** 0.3 mg PFS DME/DR Mar 2018	RG1594	**Ocrevus** PPMS & RMS, Jan 2018	RG6013	**Hemlibra** hemophilia A FVIII inh (ped/adults), Mar 2018
RG435	**Avastin** Ovarian ca FL Jun 2018	RG1273	**Perjeta + Herceptin** HER2+ BC adj, Jul 2018	RG7159	**Gazyva** CD20+ FL, Jul 2018
RG6013	**Hemlibra** hemophilia A FVIII non-inh, Oct 2018	RG6013	**Hemlibra** hemophilia A FVIII inh (ped/adults) Feb 2018	RG7446	**Tecentriq** 2L NSCLC, Jan 2018
RG6013	**Hemlibra** Q4W hemophilia A Oct 2018	RG7601	**Venclexta + Rituxan** r/r CLL, Nov 2018	RG1273	**Perjeta + Herceptin** HER2+ BC adj, Oct. 2018
RG7446	**Tecentriq+chemo+Avastin** 1L non-sq NSCLC Dec. 2018	RG1569	**Actemra auto injector** RA/GCA, Mar 2018	RG6013	**Hemlibra** hemophilia A FVIII non-inh, Dec 2018
RG7601	**Venclexta + Rituxan** r/r CLL Jun 2018	RG1569	**Actemra** CRS Sep 2018	RG6013	**Hemlibra** Q4W hemophilia A, Dec 2018
RG7601	**Venclexta + HMA/LDAC** 1L AML Nov. 2018			RG7446	**Tecentriq + other anti-tumor drugs** 1L NSCLC, Dec 2018
RG105	**Rituxan** pemphigus vulgaris, Jun 2018				
RG3648	**Xolair PFS** Asthma & CIU Sep 2018				
RG1569	**Actemra auto injector** RA, Nov 2018				
RG6152	**Xofluza** Influenza, Oct 2018				

New Molecular Entity (NME)
Additional Indication (AI)
Oncology
Immunology
Infectious Diseases
CardioMetabolism
Neuroscience
Ophthalmology
Other

Status as of January 31, 2019

Major pending approvals 2019

Pending Approval

US		EU		Japan-Chugai	
RG7596	**polatzumab vedotin** r/r DLBCL Filed Dec 2018	RG7596	**polatzumab vedotin** r/r DLBCL Filed Dec 2018	RG1569	**Actemra** CRS, Filed May 2018
RG7446	**Tecentriq + nab-paclitaxel** 1L non sq NSCLC Filed Nov 2018	RG6013	**Hemlibra** hemophilia A FVIII non-inh, Filed Apr 2018	RG1569	**Actemra** Adult Onset Still's disease, Filed May 2018
RG7446	**Tecentriq + nab-paclitaxel** 1L TNBC Filed Sep 2018	RG6013	**Hemlibra** Q4W hemophilia A, Filed Apr 2018	RG7446	**Tecentriq + nab-paclitaxel** 1L TNBC Filed Dec 2018
RG7446	**Tecentriq + chemo** 1L extensive stage SCLC Filed Sep. 2018	RG7446	**Tecentriq + chemo + Avastin** 1L non-sq NSCLC Filed Feb 2018	RG7446	**Tecentriq + chemo** 1L extensive stage SCLC Filed Sep 2018
RG6268	**entrectinib** NSCLC ROS1+ Filed Dec 2018	RG7446	**Tecentriq + nab-paclitaxel** 1L non sq NSCLC Filed Oct 2018	RG6268	**entrectinib** NTRK+ solid tumors Filed Dec 2018
RG6268	**entrectinib** NTRK1 pan-tumor Filed Dec 2018	RG7446	**Tecentriq + nab-paclitaxel** 1L TNBC Filed Sep.2018		
		RG7446	**Tecentriq + chemo** 1L extensive stage SCLC Filed Sep. 2018		
		RG6268	**entrectinib** NSCLC ROS1+ Filed Jan 2019		
		RG6268	**entrectinib** NTRK1 pantumor Filed Jan 2019		
		RG105	**MabThera** pemphigus vulgaris, Filed Feb 2018		

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Status as of January 31, 2019

Roche

Doing now what patients need next

EXHIBIT 28

REDACTED IN ITS ENTIRETY

EXHIBIT 29

REDACTED IN ITS ENTIRETY

EXHIBIT 30

REDACTED IN ITS ENTIRETY